DEVELOPMENT AND EVALUATION OF REACTIONS UTILIZING UNIQUELY SELECTIVE ELECTROPHILIC Pd CATALYSTS

by

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ABSTRACT

The Heck reaction is an important tool in target-directed syntheses, but its full potential has yet to be realized due to limited substrate compatibility. This limitation arises from poor behavior of the selectivity-determining steps of migratory insertion and β-hydride elimination when using electronically nonbiased substrates. The inability to accommodate nonbiased alkenes is due to chemist's poor understanding of the controlling factors in these two key mechanistic steps. Herein are described Pd^0 and Pd^{II} catalysts that exhibit unique selectivity in these electronically nonbiased molecular systems.

Chapter 1 describes the use of an electrophilic Pd^{II} catalyst to install two identical aryl groups upon terminal aliphatic olefins. The use of the same system, with a different aryl source, led to the discovery that electrophilic Pd^{II} catalysts are capable of selectively delivering (*E*)-styrenyl products from electronically nonbiased olefins.

Chapter 2 details optimization of the Pd^{II} system to selectively deliver traditionally inaccessible (*E*)-styrenyl products, and evaluation of substrate scope. Mechanistic experiments are performed, suggesting that the unique selectivity observed is attributable to the cationic nature of the catalyst, that the ligand on Pd is required for catalyst stability, and that the catalyst distinguishes between β-hydrogens on the basis of C–H bond strength. These findings are applied to rational design of a Pd^0-catalyzed Heck reaction of similar substrates.

The Pd^0-catalyzed system exhibits greater functional group tolerance than the oxidative system, is operationally simple, and requires no added stabilizing ligand. The design and study of this reaction is the subject of Chapter 3. Mechanistic studies suggest that solvent choice is crucial in allowing the metal center to distinguish between β-hydrogens on the basis of their relative hydridic nature.

The insight gained in the work described in Chapters 2 and 3 allowed for the rational design of a system enabling enantioselective Heck reactions using acyclic substrates. This methodology, described in Chapter 4, was intended to deliver optically active β-aryl ketones from allylic alcohol substrates. After establishing that the reaction performs as anticipated, it was applied to the unprecedented single-step enantioselective synthesis of γ-aryl ketones, and aldehydes, and a δ-aryl aldehyde.

Dedicated to my family

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LIST OF ABBREVIATIONS

3 Å MS	three angstrom molecular sieves
Ac	acetyl
aq.	aqueous
bipy	bipyridine
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
*i*Bu	*iso*-butyl
*t*Bu	*tert*-butyl
°C	degrees Celcius
calcd.	calculated
Cbz	carboxybenzyloxy
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform
cm	centimeter
d	doublet
DCE	1,2-dichloroethane
dd	doublet of doublets
ddd	doublet of doublet of doublets

dt	doublet of triplets
DMAP	4-dimethylaminopyridine
DMA	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
dmphen	2,9-dimethyl-1,10-phenanthroline
dr	diastereomeric ratio
EDG	electron donating group
ee	enantiomeric excess
equiv	equivalents
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
FTIR	Fourier transform infrared spectroscopy
g	gram
GC	gas chromatography
h	hour
HRMS	high resolution mass spectroscopy
Hz	Hertz
IPA	2-propanol

IR	infrared spectroscopy
L	liter
$LiAlH_4$	lithium aluminum hydride
m	multiplet
M	molar
m	meta
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
μL	microliter
mmol	millimole
μmol	micromole
mol	mole
mp	melting point
MS	mass spectrometry
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
o	ortho
OAc	acetate

obsvd.	observed
OTf	trifluoromethanesulfonate
OTs	toluenesulfonate
p	para
Ph	phenyl
phen	1,10-phenanthroline
PMP	1,2,2,6,6-pentamethyl-4-piperidinol
ppm	parts per million
*i*Pr	*iso*-propyl
PyrOx	pyridine oxazoline
q	quartet
Quinox	quinoline oxazoline
R_f	retention factor
rt	room temperature
s	singlet or second
SDC	sodium dodecylsulfate
SEM	2-(trimethylsilyl)ethoxy)methyl
SFC	supercritical fluid chromatography
t	triplet
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TOF	time of flight

tol	toluene
vs	versus

ACKNOWLEDGEMENTS

To accomplish the research described herein required a great deal of hard and trying work, and would have been impossible without the advice, criticism, inspiration, friendship, and good times provided by a great number of people. First, my advisor Matt Sigman has my deep gratitude for providing all of the above. He has been a source of the enthusiasm that I have sometimes lacked, a wise advisor who was greatly needed, a motivator when I was lacking, and has showed understanding when commiseration was required. It is obvious to anyone who knows Matt that he cares deeply about both science and his students. This palpable enthusiasm compels excellence in those who have the privilege to be mentored by him. Matt has encouraged me to pursue projects, both successful and failed, which he saw as questionable investments of energy and resources. By doing this he has allowed me to craft my own higher education, which instilled in me a creativity not innate to my personality.

Coworkers, both past and present, have been crucial to my success. In general, I would like to thank all of my colleagues at the University of Utah for providing inspiration, criticism, and friendship. In particular, I would like to thank Brian Michel and Katrina Jensen for providing exemplary role models as graduate students. I would also like to thank both them, and their respective spouses, Katie Michel and Nick Stadler, for being wonderful friends, and showing me how to have a great time in what has to be

one of the stranger states in the US. I would like to thank Ryan DeLuca and Ben Stokes, both for their friendship, and their assistance in producing this document.

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Most of all I would like to thank my wife, Amanda. She has constantly inspired me by excelling at a job that is much more trying and difficult than my own. She has shown incredible patience and understanding by enduring both the schedule that this education has required of me, and my berating of the more truculent molecules described herein. The lifestyle of graduate students is physically, mentally, and emotionally demanding; however we have chosen this path, while our spouses have not. I am eternally indebted to Amanda for supporting me these last five years, in more ways than can be described here. She has made me incredibly happy, and I am grateful for the courage she showed in choosing to join me here.

CHAPTER 1

DEVELOPMENT AND EVALUATION OF A PD^{II}-CATALYZED 1,1-DIARYLATION OF TERMINAL OLEFINS

Introduction

Methods for the chemo-, regio-, and stereo-selective formation of multiple bonds in a single step have the potential to improve the efficiency of target-directed synthesis, since such reactions result in rapid introduction of the molecular complexity present in the target. Olefins serve as excellent substrates for difunctionalization reactions, or those reactions which result in the formation of two new bonds in a single step. Their utility as substrates for such reactions is exemplified by the ubiquitous use of transformations such as the Diels-Alder reaction,[1-4] and Sharpless asymmetric dihydroxylation[5,6] in target-directed synthesis. Given the proven success of such complexity-building reactions in application to synthesis, there is great interest in the development of new bond-construction strategies, including those relying on transition metal catalysis. Palladium catalysis holds potential for the development of such reactions, but progress in this area of study has been hindered due to the propensity of Pd^{II}-σ-alkyls to undergo rapid β-hydride elimination.[7] This results in the liberation of the substrate as a monofunctionalized olefin, rather than the Pd^{II}-σ-alkyls undergoing further bond forming reactions required for difunctionalization (Figure 1.1). Significant progress has been

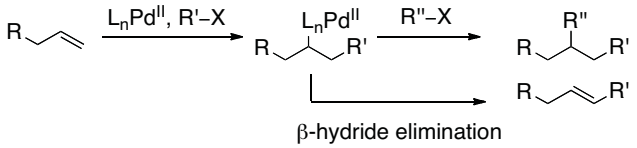


Figure 1.1. Pd^{II}-catalyzed difunctionalization of olefins, and competing β-hydride elimination.

made in the fields of palladium-catalyzed alkene dialkoxylation,[8-12] diamination,[13-17] and hydrofunctionalization,[18-23] but progress in the installation of multiple carbon-carbon bonds in a single step has been limited. Several strategies have been devised and executed to successfully avoid β-hydride elimination, which generally fall into three broad categories. First, the substrate may be designed such that the initial functionalization results in Pd^{II}-σ-alkyls that lack *syn* β-hydrogens (which are required for elimination) as exemplified in Figure 1.2.[24] Second, the Pd center may undergo alternative reactivity, frequently rapid oxidation to high oxidation state Pd, which is then functionalized to give the desired product (Figure 1.3).[25] Finally, the Pd^{II}-σ-alkyl may be stabilized by the substrate, which delays β-hydride elimination sufficiently to allow for alternative reactivity (Figure 1.4).[26]

The Sigman group is interested in developing synthetically useful methods, which deliver difunctionalized products from olefin starting materials, and has found success using the strategy dependant on the stabilization of Pd^{II}-σ-alkyls. Specifically, the exploitation of the greater stability imparted by π-benzyl and π-allyl intermediates has led to the development of Pd^{II}-catalyzed oxidative difunctionalization reactions of olefins. This chapter focuses on the development of 1,2- and 1,1-diarylation reactions of olefins wherein the two newly installed aryl groups are identical.

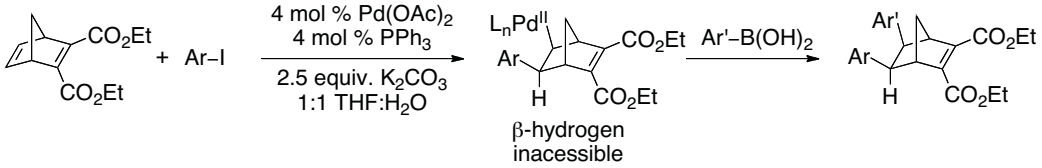


Figure 1.2. Olefin difunctionalization enabled due to lack of accessible β-hydrogens.

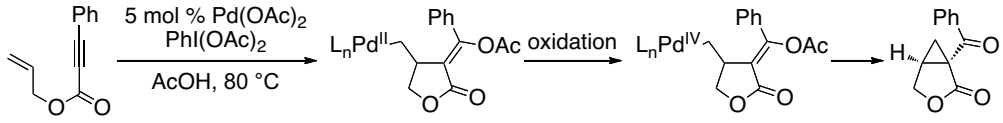


Figure 1.3. Olefin difunctionalization enabled by rapid oxidation of Pd^{II}-σ-alkyl.

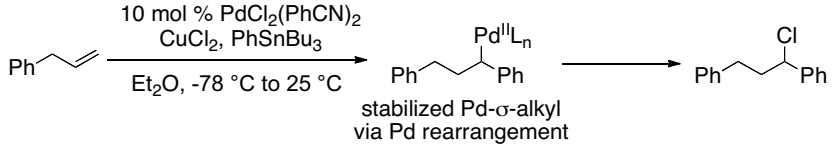


Figure 1.4. Olefin difunctionalization via stabilized Pd^{II}-σ-alkyl.

Background

The Sigman group,[27] and others,[28] have noted the potential of a diverted oxidative Heck reaction process to deliver alkene difunctionalization products. The mechanism (simplified version shown in Figure 1.5) of this reaction begins with transmetalation of Pd^{II} with an organometallic reagent to deliver **A**. Coordination and migratory insertion into the olefin substrate gives an unstable Pd-σ-alkyl intermediate, **C**. β-Hydride elimination occurs, liberating the product and Pd^0, which must be reoxidized to give the active catalyst. The potential for installing multiple bonds using this mechanistic strategy

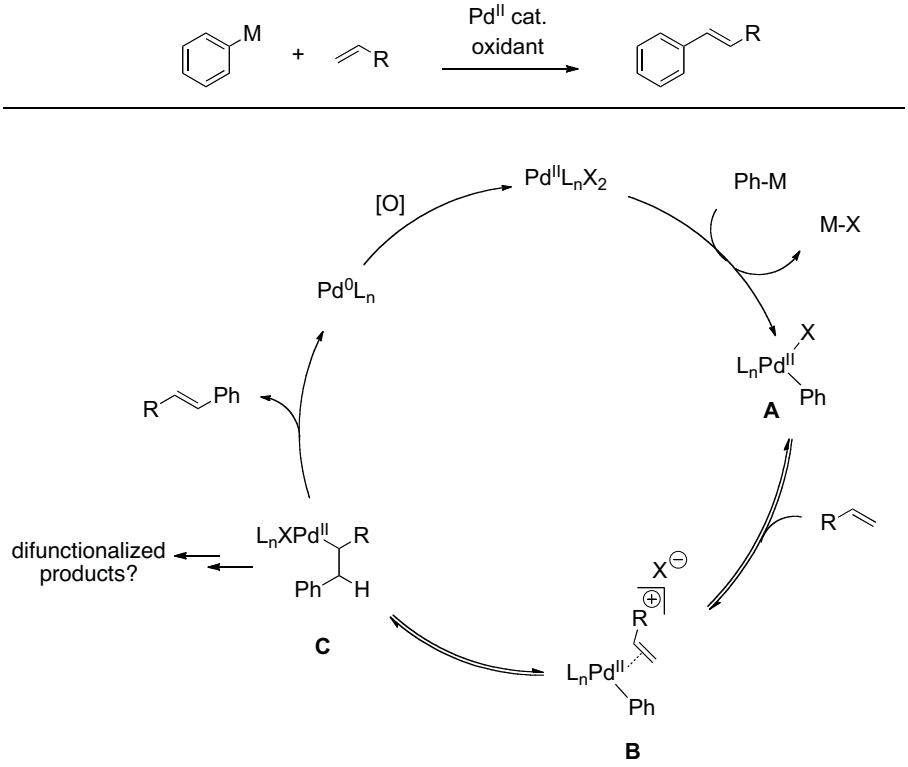


Figure 1.5. Simplified mechanism of the oxidative Heck reaction, and the intermediate key to successful difunctionalization reactions.

necessarily focuses on diverting intermediate **C** toward alternative reactivity, avoiding β-hydride elimination. As discussed below, this result may be achieved using carefully chosen catalytic conditions.

The Sigman group first noted the difunctionalization of an olefin substrate as a byproduct of a Pd^{II}-catalyzed hydroarylation reaction of styrenes (Figure 1.6).[19] The mechanism leading to the formation of this unusual product is initiated by transmetalation with an organostannane, followed by a Heck insertion[29] to deliver intermediate **C**. This intermediate is stabilized by an interaction of the metal center with the π electrons of the adjacent arene, as depicted in **D**, which delocalizes the unstable Pd–C bond, and renders it lower in energy compared to a Pd^{II}-σ-alkyl without such adjacent functionality.[30-34]

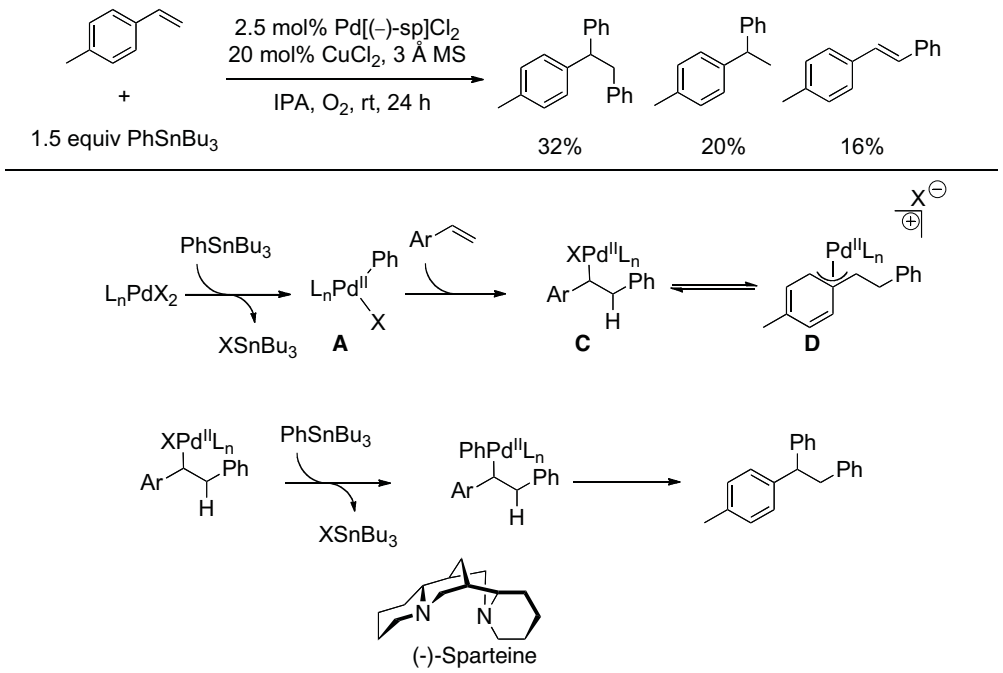


Figure 1.6. 1,2-Diarylation of styrenes, and mechanism of formation.

Additionally, when using a bidentate ligand such as sparteine, the π-electrons occupy the fourth coordination site of the metal, so that β-hydride elimination would require dissociation of either the π-system or of one of the nitrogenous ligands. By imparting this stability, the lifetime of this intermediate is increased sufficiently to allow the metal center to react with a second organostannane molecule in a transmetalation event, which is then followed by reductive elimination to deliver the 1,2-diarylated byproduct. While the conditions described delivered a poor yield of the diarylation product, the unusual mechanism of product formation, and the potential biological relevance of the products[35-37] compelled a former graduate student in the Sigman group, Dr. Kaveri Balan, to pursue the optimization of this reaction.

After extensive optimization, conditions resulting in the isolation of the 1,2-diarylation product in excellent yield were identified (Figure 1.7).[27] The major changes from the initial conditions included the use of *N,N*-dimethylacetamide (DMA) as solvent, the replacement of sparteine as the ligand with an *N*-heterocyclic carbene (I^iPr), and the use of weakly-coordinated counterions (OTs and OTf) on the Pd catalyst. Each of these features are proposed to play a specific and important role in the success of the reaction. Changing solvents from isopropanol (IPA) to DMA deprives the catalyst of a high concentration of accessible hydrides (Pd–H, leading to hydrofunctionalization in the system depicted in Figure 1.6, arises from Pd-catalyzed alcohol oxidation),[18,38-40] which greatly diminishes the amount of hydroarylation product delivered. The carbene ligand present on the metal center is highly σ-donating, which stabilizes the electrophilic catalyst, preventing catalyst decomposition.[41,42] Finally, the weakly-coordinating counterions render the metal center cationic and highly electrophilic, which results in a favorable Pd-π-benzyl intermediate[30-34] due to π-electron donation from the adjacent arene, and also favors binding of the olefin.

During this study, an interesting byproduct was observed arising from **D** slipping to an η^1 Pd-alkyl (**E** in Figure 1.8), followed by β-hydride elimination and olefin reinsertion to give a new Pd-π-benzyl **H**. This is proposed to undergo a second transmetalation followed by reductive elimination to give the 1,1-alkene diarylation product.[27] It was observed that the relative (to 1,2-alkene diarylated product) amount of this byproduct increased with decreasing electron density present in the styrene substrate, and it was hypothesized that the relationship was linear in nature. The observation of a linear free energy relationship ($\rho = -0.88$) between the electronic nature of the styrene

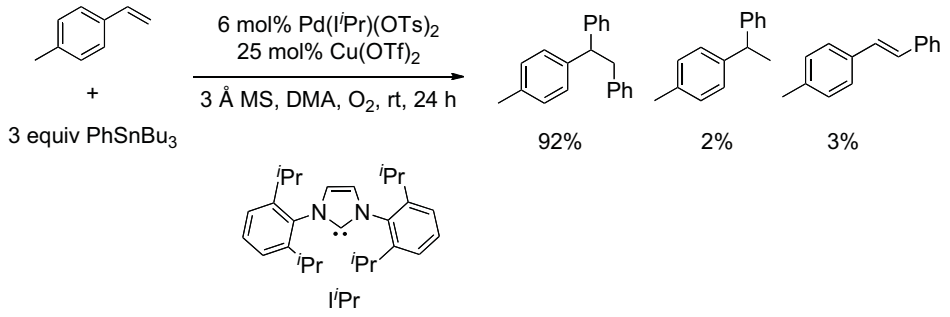


Figure 1.7. Optimized 1,2-diarylation of styrenes.

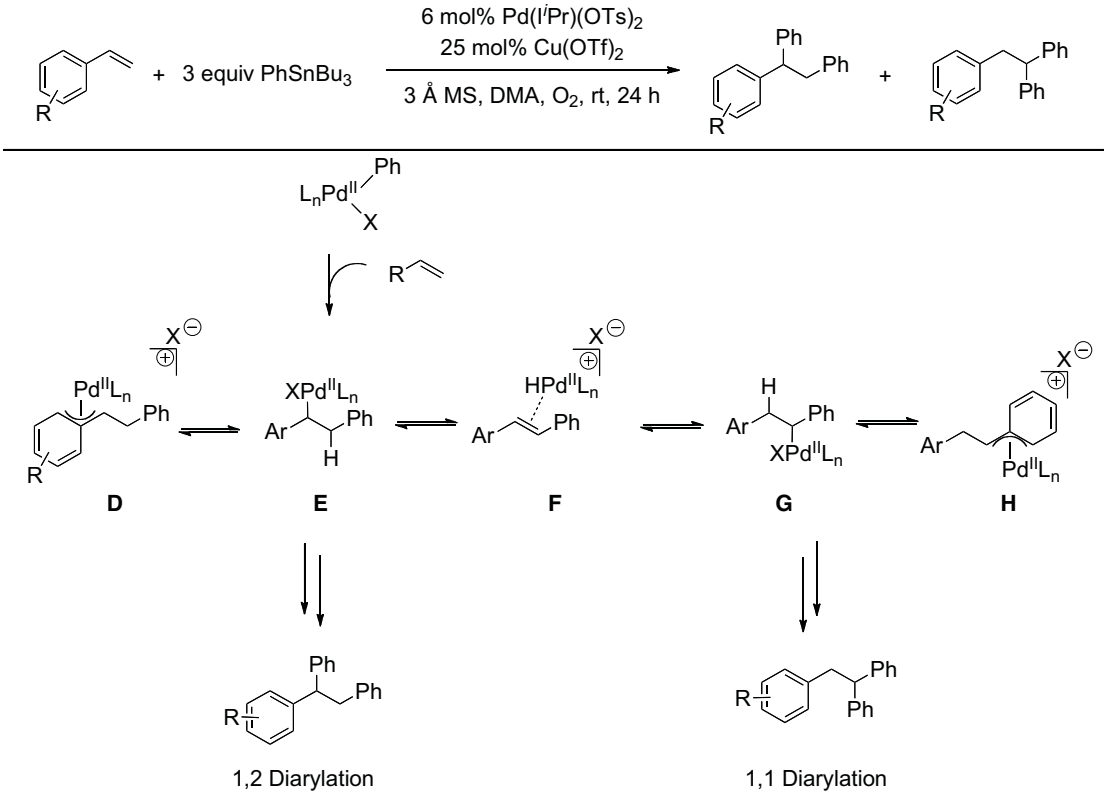


Figure 1.8. 1,1-Diarylation side product and mechanism of formation.

substrates and the ratio of these two products revealed the reaction's high level of sensitivity to the stability of π-benzyl intermediates.

Hypothesis for aliphatic olefins

The observation that 1,1- vs 1,2-diarylated product distribution in the reaction described above was dictated by the electron density of the proposed π-benzyl intermediates led to the hypothesis that novel methodology could be developed utilizing aliphatic olefin substrates in the place of styrenes. This was based on the proposal that alkyl-substituted olefins would give exclusively 1,1-diarylated products, since the substrate cannot provide π-benzyl stabilization, but this interaction would be accessible with the arene originating from the aryl stannane via palladium migration. Central to this proposal was the idea that, under carefully chosen conditions, the palladium catalyst would selectively migrate to the benzylic position rather than produce a mixture of monoarylated olefin products via non-selective β-hydride elimination. To evaluate this hypothesis, 1-nonene was subjected to the conditions optimized for 1,2-diarylation of styrenes and this indeed resulted in the formation of the desired 1,1-diaryl product, **1** (Figure 1.9).[27]

Similarly to that proposed for the 1,1-diarylation mechanism described above, the proposed mechanism for this reaction is initiated by a Heck insertion, followed by β-hydride elimination to give **J**. Hydride insertion at the position β to the arene would lead to **K**, which can be stabilized as a π-benzyl intermediate. A second transmetalation is proposed to occur followed by reductive elimination to provide the 1,1-diarylation product. Since the diarylmethine core structure is a common motif in biologically active

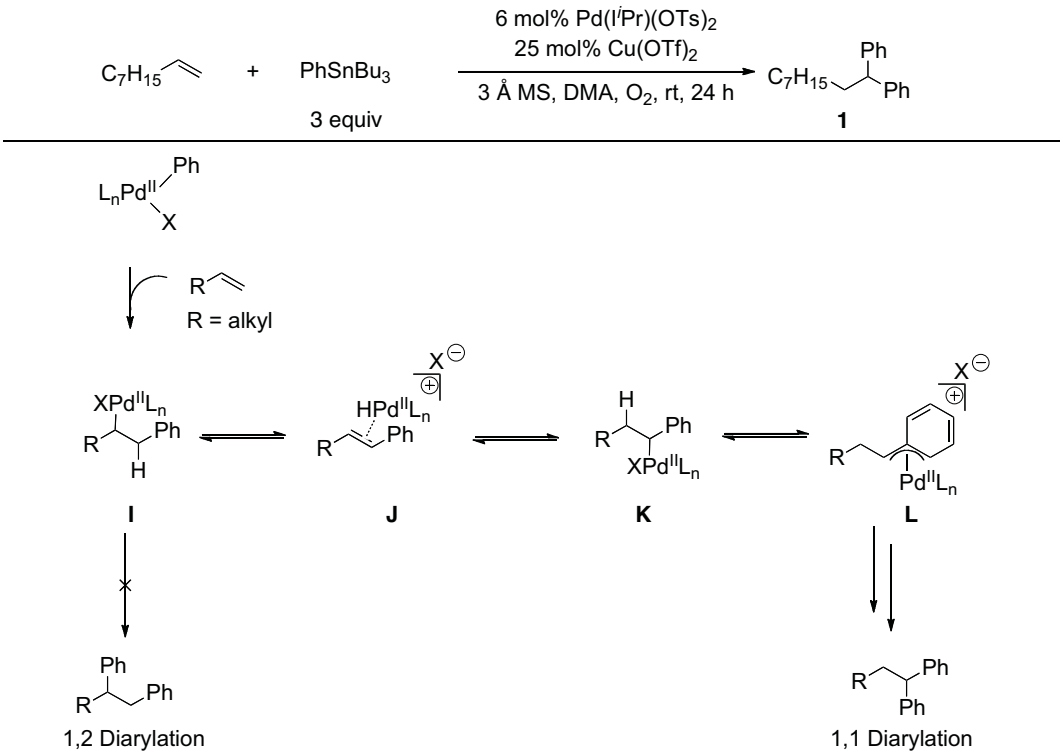


Figure 1.9. Hypothesized 1,1-diarylation of aliphatic olefins.

compounds, it seemed valuable to pursue this initial result and to determine the scope and limitations of this new methodology.

Optimization and Evaluation of Substrate Scope

Given the propensity of the previously published reaction to give undesired byproducts when electron deficient arenes were used, attempts were made to optimize the new 1,1-diarylation reaction of terminal olefins for use with electron deficient arylstannanes. These optimization attempts included the evaluation of varying reaction concentrations, copper loadings, the use of counterions with varying coordinative abilities, varying temperature, and the use of different solvents. Ultimately, the previously optimized conditions could not be improved upon, and better yields using electron deficient arenes were not achieved. Using the optimal conditions previously

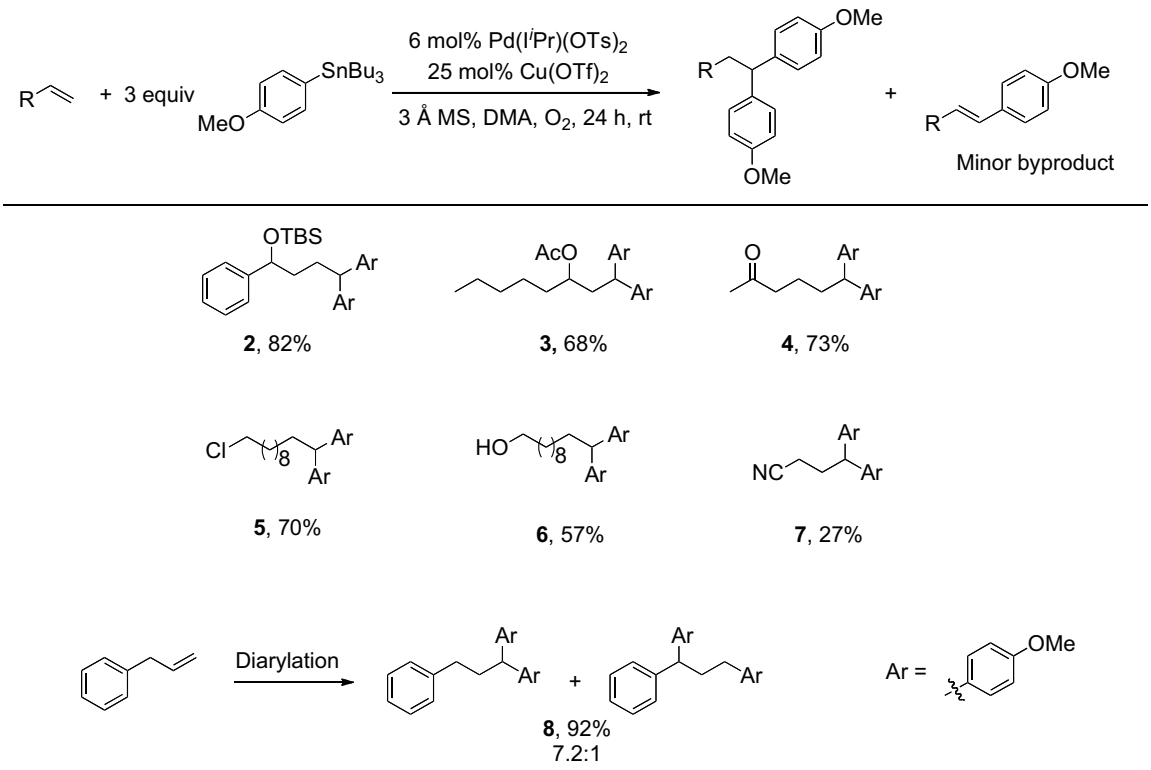


Figure 1.10. Scope of 1,1-diarylation; alkene component.

reported, this reaction was found to be quite tolerant of functional groups commonly encountered in organic synthesis (Figure 1.10).

A substrate bearing a protected homoallylic alcohol leads to a good yield of the desired product (**2**). Similiarly, a protected allylic alcohol undergoes the diarylation reaction cleanly to give **3** with no products derived from Pd-π-allyl chemistry observed.[43] Substrates containing a ketone or ester are well tolerated, as are primary chlorides (leading to **4**, **3**, and **5**, respectively). A substrate with a distal free alcohol resulted in moderate yields of the 1,1-diarylation product (**6**), but allyl cyanide is a poor substrate for this reaction, providing a 27% yield of **7**. This is likely due to the Lewis basic nature of nitriles, which presumably bind to the electrophilic catalyst, attenuating reactivity. Allyl benzene gives a high yield of diarylation products as a mixture of regioisomers (**8**).

Enhancing the synthetic potential of this transformation, an enantioenriched sample of **9** suffered no erosion in enantiomeric excess when converted to **3** using these conditions (Figure 1.11). This provides evidence, though not conclusive, that the palladium catalyst does not engage the β-hydride at the stereocenter, as this may result in racemization.

Next, the scope of the aryl stannane component of the reaction was evaluated (Figure 1.12). The reaction proceeds well using a *p*-alkyl phenyl stannane, giving **10,** and $PhSnBu_3$, resulting in **11**. *p*-Fluoro phenyl stannane gave a slightly diminished yield of **12**, while use of more electron poor *p*-chloro phenyl stannane resulted in a further decrease in yield. Using the highly electron deficient aryl stannane bearing a trifluromethyl group gave low yield with a greater amount of the Heck product, and poor tolerance of steric hindrance in the aryl stannane was observed giving **15** in only 26% yield. The major byproducts for these reactions are oxidative Heck products,[44-48] presumably arising from Pd-dissociation from intermediate **J** (Figure 1.9), the yields of which are also reported in Figure 1.12.

Unsuccessful 1,1-alkene diarylation reactions

Several of the reactions performed in the scope evaluation failed completely, or gave such poor results that the products were not isolated. For example, submission of a substrate bearing a bromine atom resulted a complex mixture of products (Figure 1.13). The submission of a TBS-protected allylic alcohol resulted in a sluggish reaction, with only minor conversion of starting material by crude NMR analysis. Submission of vinyl stannanes did not give the desired product, instead giving complex mixtures of products, and a tosyl protected homoallylic amine gave only trace product by crude NMR analysis.

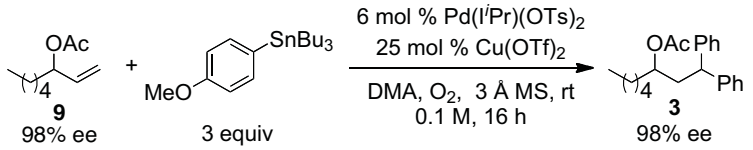


Figure 1.11. Enantioenriched **9** suffers no erosion of enantiomeric excess when submitted to the 1,1-diarylation reaction.

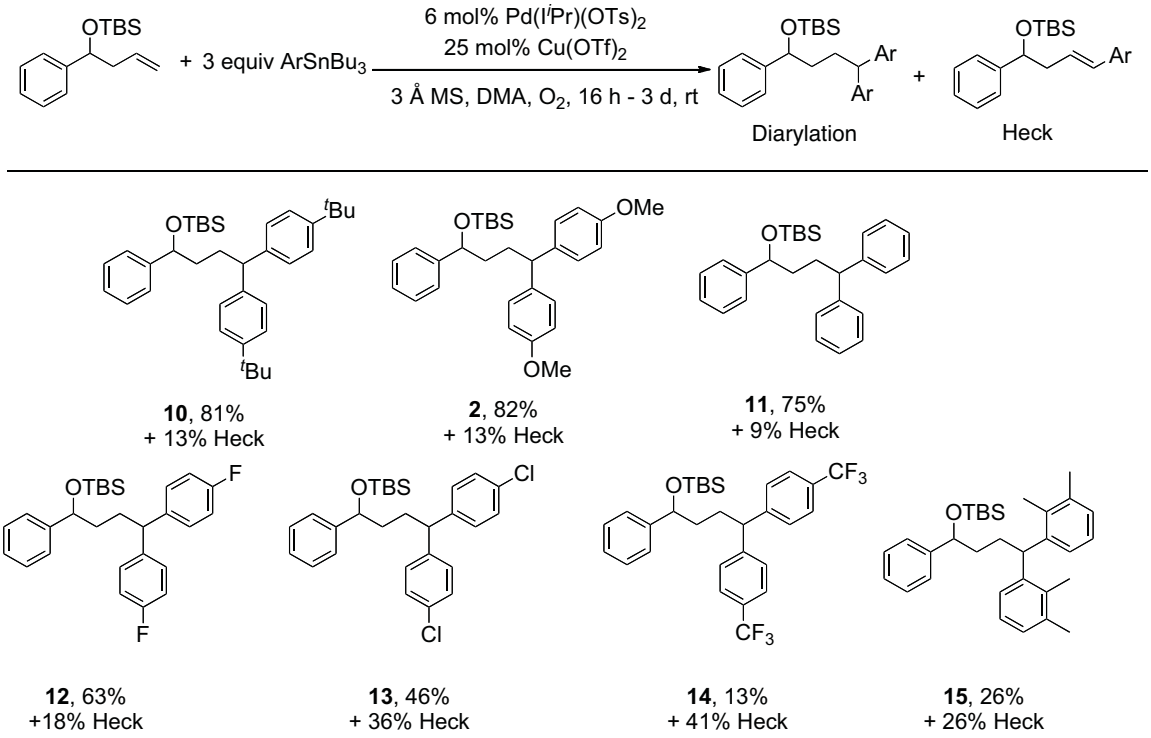


Figure 1.12. Scope of 1,1-Diarylation; arylstannane component.

Mechanistic Analysis and Initial Result for Oxidative Heck Reaction

Evaluation of the scope of the aryl stannane revealed a clear trend between the electronic nature of the aryl stannane and the yields of both the 1,1-diarylation and oxidative Heck products. Specifically, as the aryl stannane became more electron deficient, the ratio of diarylation product to the oxidative Heck product decreased. This intriguing observation led to experiments probing whether there was a direct relationship

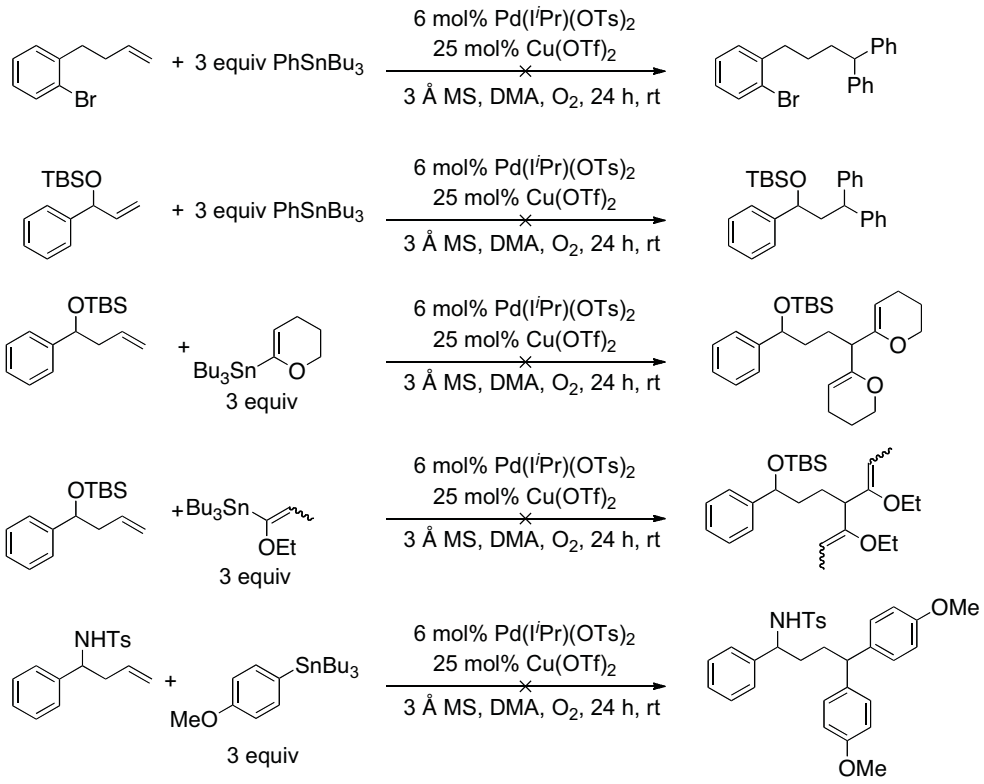


Figure 1.13. Failed, or poorly performing 1,1-alkene difunctionalization reactions.

between these parameters. In this pursuit, a variety of electronically disparate arylstannanes were submitted to the described cross coupling to give products such as those shown in Figures 1.11 and 1.12, along with the Heck byproducts. The ratios of 1,1-diarylation to Heck products was determined by ^{1}H NMR integration performed on a mixture from which the tin byproducts had been chromatographically removed. Plotting log[1,1-diarylation]/[Heck] as a function of the Hammett parameters of the aryl stannane substituents (σ) indeed revealed a linear free energy relationship with a ρ = -0.91 (Figure 1.14).

This relationship can be explained by noting that the cationic metal center is stabilized by the π-electrons of the aryl group in π-benzyl structure **L** (Figure 1.9), and

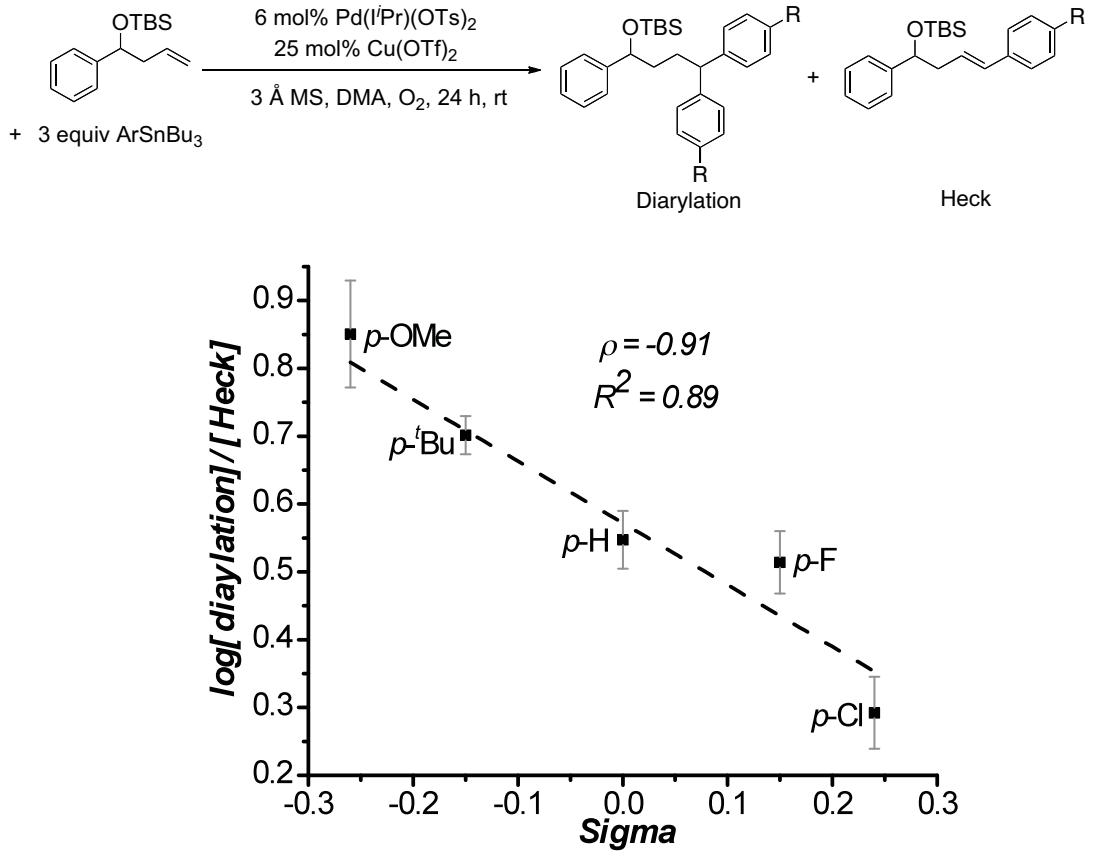


Figure 1.14. Hammett analysis of 1,1-diarylation reaction.

that electron rich arenes provide more stability and impart a longer lifetime to this intermediate than electron poor arenes. This slows β-hydride elimination, allowing for a second transmetalation, which results in a higher ratio of 1,1-diarylation to oxidative Heck products when electron rich aryl stannanes are used. When electron deficient arenes are used, they provide insufficient π-benzyl stabililzation to impart the lifetime required by these intermediates to undergo a second transmetalation. This results in dissociation of the olefin, and isolation of the Heck product. It is interesting to note that despite the different products delivered by the 1,2- and 1,1-diarylation reactions, the slope of the two Hammett plots are nearly identical (ρ = –0.88 for the system leading to

1,2-diarylation),[27] suggesting that they are affected to a similar degree by the stability of Pd-π-benzyl intermediates.

While the described methodology provided the only currently existing access to 1,1-diarylated products from olefins in a single step, it does have practical disadvantages. First, the products are limited by the mechanism of this transformation to those bearing identical arenes in a 1,1-relationship. This shortcoming was subsequently addressed by arriving at the requisite Pd^{II} species via oxidative addition, followed by transmetalation using organometallic reagents.[49] An additional disadvantage is that the reagents used are somewhat unattractive, as structurally diverse arylstannanes are not commercially available, can be inconvenient to prepare, and are well known to be toxic. In contrast, many aryl boronic acids are commercially available, and the byproducts are environmentally benign. For this reason, their use in the place of arylstannanes was explored, but subjugation of these reagents to the previously optimized conditions resulted in a complex mixture of products. However, submission of the corresponding ethyene glycol aryl boronic ester analogues resulted in clean formation of a single product, albeit surprisingly not that resulting from the desired 1,1-diarylation (Figure 1.15). Instead, a moderate yield of the oxidative Heck product, **16**, was observed, with the remainder of the mass balance being unreacted starting material.

Initial result for (*E*)-styrenyl selective oxidative Heck reaction

At first glance, the discovery of an additional method to access well-known oxidative Heck products may not be of value to the synthetic community. However, several observations compelled the further exploration of this method. The first was the

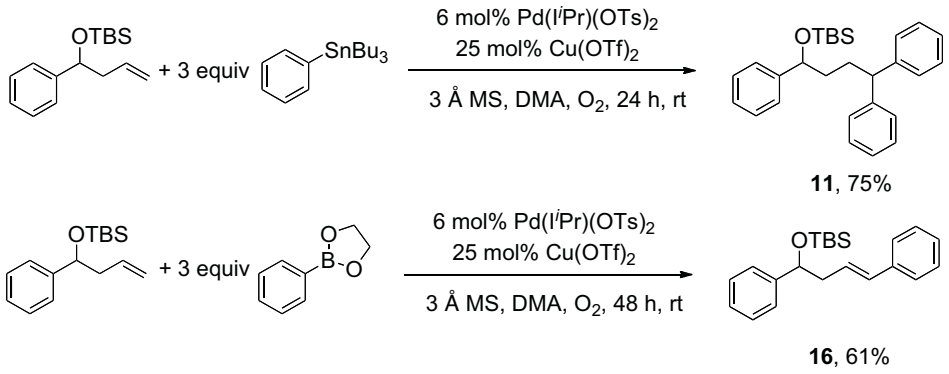


Figure 1.15. 1,1-Diarylation vs. oxidative Heck products arising from the use of different transmetalating agents under otherwise identical conditions.

observation of a single (*E*)-styrenyl product (see Chapter 2 for a detailed discussion of selectivity in Heck reactions) when a homoallylic alcohol derivative was used, although substrate chelation, as nicely demonstrated by the White group,[50] and others,[51-54] may be responsible for the observed selectivity. While it seemed unlikely that substrate chelation dictated product selectivity, given the bulky silyl ether,[55] this possibility could not be ruled out. Therefore, at a relatively early stage of development, several unfunctionalized and distally functionalized terminal alkene substrates were evaluated, and were found to give nearly exlusive formation of the (*E*)-styrenyl products, suggesting that chelation was not responsible for the observed selectivity (Figure 1.16). The vast majority of Heck reactions are performed on electronically biased substrates. In this case, neither electronic bias nor chelation was found to be required, which compelled the extensive exploration of this unanticipated result, as described in Chapter 2.

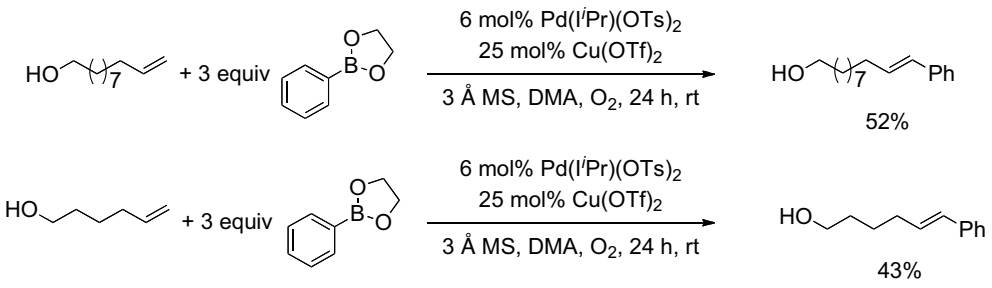


Figure 1.16. Submission of substrates unlikely to participate in catalyst chelation.

Conclusions

In conclusion, a 1,1-selective diarylation reaction of terminal alkenes was developed, found to be tolerant of diverse functionality, and the reaction was demonstrated not to erode enantiomeric excess in a substrate with a proximal stereocenter. The reaction performs well using electron-rich aryl stannanes, but yield and selectivity suffer when the aryl stannane is electron-deficient or sterically hindered. A linear free energy relationship was observed demonstrating the reaction's high sensitivity to Pd-π-benzyl stability. The described reaction suffers from inherent disadvantages, including the limitation to the installation of two identical arenes, and from the unattractive nature of the organostannane reagents used. In order to address the second shortcoming, aryl boronic acid derivatives were submitted to the conditions optimized for 1,1-diarylation, but were found to give no 1,1-diarylation product. Instead, the reaction delivered only (*E*)-styrenyl products when using traditionally challenging Heck substrates. This observation led to the discovery and development of the reaction described in Chapter 2.

Experimental

General considerations

Dry dimethylacetamide (DMA) was purchased from Aldrich and stored over activated 3 Å molecular sieves (3 Å MS), Tetrahydrofuran (THF) and dichloromethane were dried before use by passing through a column of activated alumina. 3 Å MS used in diarylation reactions were powdered and activated by heating with a Bunsen burner while under vacuum. Terminal olefins were purchased from Aldrich or Acros, or synthesized according to the procedures referenced. Mg was purchased from Acros. Bu_3SnPh and Bu_3SnCl were purchased from Gelest Inc. Palladium(II) chloride was purchased from Pressure Chemicals. (*S*)-1-Octene-3-ol was purchased from Fluka. $[Pd(allyl)Cl]_2$, $[Pd(I^iPr)Cl_2]_2$[56] and $Pd(I^iPr)(OTs)_2$[27] were synthesized according to literature procedures. ^{1}H-NMR spectra were obtained at 300 MHz, chemical shifts are reported in ppm, and referenced to the $CHCl_3$ singlet at 7.26 ppm or to the center peak of the CD_2Cl_2 triplet at 5.32 ppm. ^{13}C-NMR spectra were obtained at 75 MHz and referenced to the center line of the $CDCl_3$ triplet at 77.23 ppm, or the center line of the CD_2Cl_2 quintet at 54.00 ppm. The abbreviations s, d, t, dd, dt, m stand for the resonance multiplicities singlet, doublet, triplet, doublet of doublets, doublet of triplets and multiplet, respectively. Thin-layer chromatography was performed with EMD silica gel 60 F254 plates eluting with solvents indicated, visualized by a 254 nm UV lamp and stained with phosphomolybdic acid. Flash chromatography was performed using EM reagent silica 60 (230-400 mesh). IR spectra were recorded using a Thermo Nicolet FT-IR. HRMS (high resolution mass spectrometry) data were obtained on a Waters LCP Premier XE instrument by ESI/TOF. Chiral GC (gas chromatography) analysis was performed using a Hewlett Packard HP

6890 Series CG system fitted with a HP-Chiral permethylated β-cyclodextrin column. SFC (supercritical fluid chromatography) analysis was performed at 40 ºC, using a Thar instrument fitted with an AD-H column.

Synthesis of terminal olefin substrates

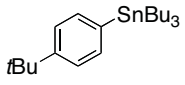
tert-Butyldimethyl((1-phenylbut-3-en-1-yl)oxy)silane,[57] oct-1-en-3-yl acetate,[58] and 11-choroundec-1-ene[59] were prepared following literature procedures and purity confirmed via ^{1}H NMR. (*S*)-1-Octene-3-ol was converted to **9** using the same procedure as that used to synthesize racemic **9**. The enantiomeric excess of **3** was determined by chiral GC (see below).

Synthesis of organostannane reagents following literature procedure

Tributyl(4-fluorophenyl)stannane,[60] tributyl(4-(methoxyphenyl)stannane,[19] and tributyl(4-chlorophenyl)stannane,[61] were prepared following literature procedures and purity confirmed via ^{1}H NMR.

General procedure for the synthesis of organostannane reagents

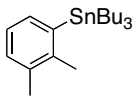
Tributyl(4-(*tert*-butyl)phenyl)stannane



To an oven-dried 50 mL round bottom flask equipped with a stir bar and water condenser was added 188 mg Mg (7.73 mmol, 1.70 equiv) and the flask was flushed with nitrogen before adding 5.0 mL THF. Two drops dibromoethane were added via syringe, followed by 1.07 g 1-bromo-4-(*tert*-butyl)benzene (5.00 mmol, 1.10 equiv) via syringe.

The mixture was heated to reflux and stirred for 24 h. A separate dry 50 mL round bottom flask equipped with a stir bar and water condenser was flushed with nitrogen. The organometallic mixture was transferred from the first flask to the second via cannula and the mixture was diluted with 5 mL THF. To this mixture, 1.48 g Bu_3SnCl (4.55 mmol) was added dropwise via syringe before heating the mixture to reflux and stirring for 24 h. The mixture was cooled to room temperature and 10 mL 1 M NaOH was added before stirring for 1 h. The mixture was transferred to a separatory funnel with 10 mL Et_2O. The aqueous layer was extracted three times with 10 mL Et_2O. The combined organic layers were washed with 25 mL H_2O and 25 mL brine before they were dried over Na_2SO_4. The mixture was filtered and the solvent removed in vacuo. The product was purified by silica gel flash chromatography eluting with hexanes and the ^1H NMR spectrum compared to that reported previously[62] to ensure purity. Yield: 92% (1.94 g).

Tributyl(2,3-dimethylphenyl)stannane

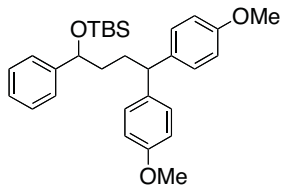


The procedure used for the preparation of tributyl(4-(*tert*-butyl)phenyl)stannane was used except 925 mg 1-bromo-2,3-dimethylbenzene (5.00 mmol, 1.10 equiv.) was added. The product was purified in the same way as tributyl(4-(*tert*-butyl)phenyl)stannane. Yield 89% (1.59 g). R_f = 0.54 w /hexanes. IR: 3050, 2955, 2923, 2870, 2853, 1463l, 1418, 1376, 1340, 1071, 1014, 960, 874, 768, 712, 667, 597 cm^{-1}. ^1H-NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.1 Hz, 9 H), 1.03-1.08 (m, 6 H), 1.34 (sextet, *J* = 7.1 Hz, 6 H), 1.47-1.57 (m, 6 H), 2.27 (s, 3 H), 2.30 (s, 3 H), 7.07-7.11 (m, 2 H), 7.22-

7.25 (m, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 10.5, 13.9, 21.2, 23.1, 27.7, 29.4, 125.6, 130.2, 134.5, 136.3, 142.7, 143.1.

General procedure for oxidative diarylation reaction

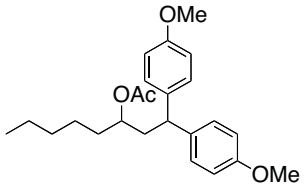
(4,4-*bis*(4-Methoxyphenyl)-1-phenylbutoxy)(*tert*-butyl)dimethylsilane (**2**)



To an oven-dried 50 mL round bottom Schlenk flask equipped with a stir bar was added 25 mg Pd(I^{i}Pr)$(OTs)_2$ (0.030 mmol, 0.05 equiv.), 45 mg $Cu(OTf)_2$ (0.013 mmol, 0.25 equiv.), and 250 mg powdered freshly activated 3 Å MS. The flask was flushed with nitrogen before adding 2.50 mL DMA. A solution of 131 mg *tert*-butyldimethyl((1-phenylbut-3-en-1-yl)oxy)silane (0.50 mmol) was added in 1.50 mL DMA via syringe. A three-way joint was fitted with a balloon of O_2 and attached to the flask. The apparatus was evacuated and refilled with oxygen three times. The mixture was stirred under O_2 atmosphere for 5 minutes. To the stirred mixture was added 596 mg tributyl(4-methoxyphenyl)stannane (1.50 mmol, 3.00 equiv.) in 0.50 mL DMA via syringe. After 16 h the mixture was filtered through celite, rinsed with 15 mL Et_2O, and transferred to a separatory funnel. Fifteen mL distilled water was added, and the aqueous layer was extracted three times with 15 mL Et_2O. The combined organic extracts were washed twice with 15 mL distilled water and 15 mL brine then dried over Na_2SO_4. The mixture was filtered and the solvent was removed in vacuo. The product was purified by silica gel flash chromatography eluting with 1% EtOAc/hexanes. For each substrate this

procedure was performed at least twice and the average isolated yield is reported. Yield 81-83% (193 mg and 197 mg); R_f = 0.46 w/ 10% EtOAc in hexanes. IR (neat): 2951, 2930, 2855, 1609, 1509, 1463, 1361, 1301, 1247, 1176, 1091, 1038, 835, 775, 701, 554 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ -0.17 (s, 3 H), 0.00 (s, 3 H), 0.88 (s, 9 H), 1.52-1.72 (m, 2 H), 1.86-2.08 (m, 2 H) 3.74 (t, *J* = 7.8 Hz, 1 H), 3.76 (s, 6 H), 4.65 (dd, *J* = 6.9, 5.4 Hz, 1 H), 6.78 (d, *J* = 8.8 Hz, 4 H), 7.05 (d, *J* = 8.7 Hz, 4 H), 7.19-7.29 (m, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ -4.7, -4.4, 18.4, 26.1, 31.7, 39.3, 49.6, 55.4, 75.0, 113.9, 113.9, 126.1, 127.0, 128.2, 128.8, 128.8, 137.8, 137.9, 145.7, 157.9. HRMS $C_{30}H_{40}O_3Si$ $(M+Na)^+$ calcd.; 499.2644 obsd.; 499.2655.

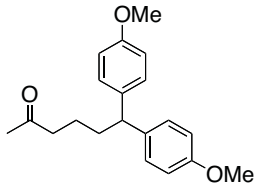
1,1-*bis*(4-Methoxyphenyl)octan-3-yl acetate (**3**)



The same procedure used to synthesize **2** was used except 85 mg oct-1-en-3-yl acetate (**9**) (0.50 mmol) was added, and the product was purified after 20 h by silica gel chromatography by eluting with 4% EtOAc in hexanes. Yield: 64-72% (123 mg and 139 mg); R_f = 0.37 w/10% EtOAc in hexanes. IR (neat) 2955, 2932, 2859, 1734, 1609, 1509, 1464, 1374, 1302, 1246, 1177, 1036, 825, 668 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.86 (t, *J* = 7.1 Hz, 3 H), 1.14-1.30 (m, 6 H), 1.48-1.58 (m, 2 H), 1.94 (s, 3 H), 2.17 (m, 1 H), 2.28 (m, 1 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 3.90 (br t, *J* = 8.0 Hz, 1 H), 4.77 (m, 1 H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2 H), 7.09 (d, *J* = 8.3 Hz, 2 H), 7.17 (d, *J* = 8.4 Hz, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.2, 21.3, 22.7, 24.8, 31.9, 34.5, 40.3, 46.3,

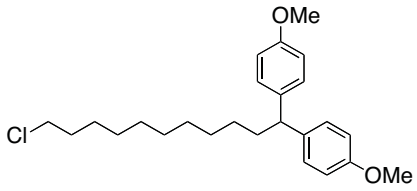
55.4, 55.4, 73.2, 114.0, 114.1, 128.7, 128.8, 137.1, 137.1, 158.0, 158.1, 170.9. HRMS $C_{24}H_{32}O_4$ $(M+Na)^+$ calcd.; 407.2198 obsd.; 407.2195.

6,6-*bis*(4-methoxyphenyl)hexan-2-one (**4**)



The same procedure used to synthesize **2** was used except 49 mg hex-5-en-2-one (0.50 mmol) was added, and the product was purified after 20 h by silica gel chromatography by eluting with 5% EtOAc in hexanes. Yield: 72-74% (112 mg and 115 mg); R_f = 0.45 w/10% EtOAc in hexanes. IR (neat) 2998, 2934, 2835, 1713, 1608, 1583, 1509, 1462, 1442, 1358, 1301, 1245, 1176, 1034, 825, 552 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.49-1.59 (m, 2 H), 1.97 (tt, *J* = 7.6, 5.1 Hz, 2 H), 2.09 (s, 3 H), 2.44 (t, *J* = 7.3 Hz, 2 H), 3.76 (s, 6 H), 3.81 (t, *J* = 7.6 Hz, 1 H), 6.82 (d, *J* = 8.6 Hz, 4 H), 7.13 (d, *J* = 8.5 Hz, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.5, 30.0, 35.6, 43.8, 49.7, 55.4, 114.0, 128.7, 137.5, 158.0, 209.1. HRMS $C_{20}H_{24}O_3$ $(M+Na)^+$ calcd.; 335.1623 obsd.; 335.1635.

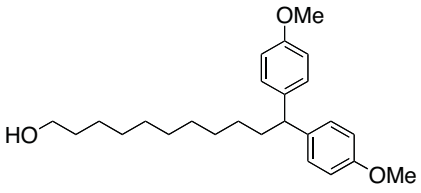
4,4'-(11-Chloroundecane-1,1-diyl)*bis*(methoxybenzene) (**5**)



The same procedure used to synthesize **2** was used except 94 mg 11-chloroundec-1-ene (0.50 mmol) was added, and the product was purified after 20 h by silica gel

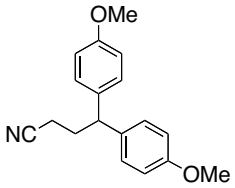
chromatography by eluting with hexanes. Yield: 65-74% (132 mg and 149 mg); R_f = 0.40 w/5% EtOAc in hexanes. IR (neat) 2996, 2927, 2854, 1609, 1509, 1497, 1463, 1441, 1301, 1246, 1218, 1177, 1037, 827, 668 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.11-1.44 (m, 24 H), 1.75 (tt, *J* = 7.8, 6.7 Hz, 2 H), 1.96 (dt, *J* = 8.1, 7.8 Hz, 2 H), 3.53 (t, *J* = 6.7 Hz, 2 H) 3.77-3.85 (m, 8 H), 6.82 (d, *J* = 8.7 Hz, 4 H), 6.86-6.95 (m, 2H), 7.14 (d, *J* = 8.7 Hz, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 27.1, 28.2, 29.1, 29.6, 29.7, 29.7, 29.8, 32.8, 36.3, 45.4, 49.8, 55.4, 55.9, 113.9, 114.9, 119.7, 128.8, 138.1, 157.9. HRMS $C_{25}H_{35}ClO_2$ $(M+Ag)^+$ calcd.; 509.1377 obsd.; 509.1396.

11,11-*bis*(4-Methoxyphenyl)undecan-1-ol (**6**)



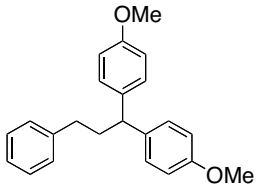
The same procedure used to synthesize **2** was used except 85 mg undec-10-en-1-ol (0.50 mmol) was added, and the product was purified after 22 h by silica gel chromatography by eluting with 10% EtOAc in hexanes. Yield: 56-57% (108 mg and 110 mg); R_f = 0.28 w/20% EtOAc in hexanes. IR (neat) 3367, 2997, 2927, 2853, 1609, 1510, 1464, 1419, 1307, 1247, 1176, 1037, 824, 668, 589 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.15-1.40 (m, 16 H), 1.55 (tt, *J* = 7.1, 6.4 Hz, 2 H), 1.96 (dt, *J* = 7.7, 6.6 Hz, 2 H), 3.63 (t, *J* = 6.6 Hz, 2 H), 3.79 (t, *J* = 8.5 Hz, 1 H), 3.77 (s, 6 H), 6.82 (d, *J* = 8.6 Hz, 4 H), 7.14 (d, *J* = 8.5 Hz, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 25.9, 28.2, 29.6, 29.7, 29.7, 29.7, 29.8, 33.0, 36.3, 49.8, 55.4, 63.3, 113.9, 128.8, 138.1, 157.9. HRMS $C_{25}H_{36}O_3$ $(M+Ag)^+$ calcd.; 491.1715 obsd.; 491.1717.

4,4-*bis*(4-Methoxyphenyl)butanenitrile (**7**)



The same procedure used to synthesize **2** was used except 35 mg allyl cyanide (0.50 mmol) was added, and the product was purified after 20 h by silica gel chromatography by eluting with 5% EtOAc in hexanes to give the product which decomposes at room temperature. Yield: 26-28% (36 mg and 40 mg); R_f = 0.40 w/ 20% EtOAc in hexanes. IR (neat) 2933, 2836, 2245, 1609, 1583, 1509, 1263, 1302, 1245, 1177, 1116, 1033, 828, 578, 552 cm^{-1}. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 2.23-2.36 (m, 4 H), 3.76, (s, 6 H), 3.94 (t, *J* = 7.8 Hz, 1 H), 6.84 (d, *J* = 8.8 Hz, 4 H), 7.15 (d, *J* = 8.6 Hz, 4 H). ^{13}C-NMR (75 MHz, CD_2Cl_2): δ 16.2, 31.8, 48.8, 55.7, 114.5, 120.1, 129.0, 136.0, 158.9. HRMS $C_{18}H_{19}NO_2$ $(M+Na)^+$ calcd.; 304.1313 obsd.; 304.1318.

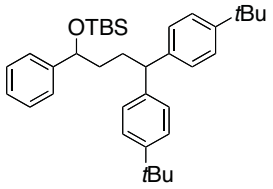
4,4'-(3-Phenylpropane-1,1-diyl)*bis*(methoxybenzene) (**8**)



The same procedure used to synthesize **2** was used except 59 mg allyl benzene (0.50 mmol) was added, and the product was purified after 22 h by silica gel chromatography by eluting with 1% EtOAc in hexanes to give a mixture of regioisomeric products in a 7.2:1 ratio. Yield: 90-93% (150 mg and 155 mg); R_f = 0.44 w/ 5% EtOAc in hexanes. IR (neat) 3026, 2999, 2932, 2834, 1609, 1510, 1455, 1301, 1246, 1176, 1036,

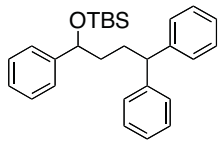
828, 700, 549 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.18-2.35 (m, 2 H), 2.48-2.59 (m, 2 H), 3.75-3.85 (m, 7 H), 6.80-6.84 (m, 3.6 H), 7.04-7.07 (m, 0.5 H), 7.13-7.30 (m, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 33.3, 34.3, 37.9, 49.1, 49.9, 55.4, 55.4, 113.9, 114.0, 126.0, 126.2, 128.0, 128.5, 128.6, 128.9, 129.0, 129.5, 134.4, 137.2, 137.6, 142.4, 145.5, 158.0, 158.1. HRMS $C_{23}H_{24}O_2$ $(M+K)^+$ calcd.; 371.1413 obsd.; 371.1429.

(4,4-*bis*(4-(*tert*-Butyl)phenyl)-1-phenylbutoxy)(*tert*-butyl)dimethylsilane (**10**)



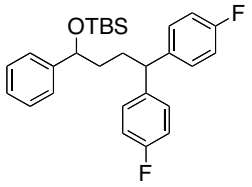
The same procedure used to synthesize **2** was used except 635 mg tributyl(4-(*tert*-butyl)phenyl)stannane (1.50 mmol) was added, and the product was purified after 20 h by silica gel chromatography by eluting with hexanes. Yield: 78-81% (206 mg and 214 mg); R_f = 0.79 w/ 5% EtOAc in hexanes. IR (neat) 3026, 2903, 2859, 1510, 1493, 1471, 1462, 1407, 1362, 1257, 1092, 864, 836, 775, 700, 579 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ -0.17 (s, 3 H), 0.00 (s, 3 H), 0.87 (s, 9 H), 1.27 (s, 18 H) 1.55-1.75 (m, 2 H), 1.96-2.09 (m, 2 H), 3.75 (dd, *J* = 8.0, 8.0 Hz, 1 H), 4.64 (dd, *J* = 5.5, 5.5 Hz, 1 H), 7.09 (d, *J* = 8.3 Hz, 4 H), 7.39-7.27 (m, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ -4.7, -4.5, 18.5, 26.1, 31.4, 31.6, 34.5, 39.2, 50.5, 75.0, 125.4, 125.4, 126.1, 127.0, 127.6, 127.6, 128.1, 142.4, 145.6, 148.7, 148.7. HRMS $C_{36}H_{52}OSi$ $(M+Na)^+$ calcd.; 551.3685 obsd.; 551.3686.

tert-Butyldimethyl(1,4,4-triphenylbutoxy)silane (**11**)



The same procedure used to synthesize **2** was used except 551 mg Bu_3SnPh (1.50 mmol) was added, and the product was purified after 23 h by silica gel chromatography by eluting with hexanes. Yield: 72-76% (151 mg and 158 mg); R_f = 0.09 w/ hexanes. IR (neat) 3061, 3026, 2950, 2928, 2856, 1600, 1506, 1493, 1471, 1451, 1361, 1255, 1093, 1070, 979, 862, 835, 804, 775, 698, 547 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ -0.17 (s, 3 H), 0.00 (s, 3 H), 0.89 (s, 9 H), 1.56-1.74 (m, 2 H), 1.96-2.19 (m, 2 H), 3.83 (dd, *J* = 7.8, 7.8 Hz, 1 H), 4.67 (dd, *J* = 5.0, 6.6 Hz, 1 H), 7.02-7.30 (m, 15 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ -4.7, -4.5, 18.4, 26.1, 31.3, 39.2, 51.4, 75.0, 126.1, 126.2, 127.0, 128.0, 128.1, 128.2, 128.6, 128.6, 145.2, 145.3, 145.6. HRMS $C_{28}H_{36}OSi$ $(M+Na)^+$ calcd.: 439.2433 obsd.: 439.2439.

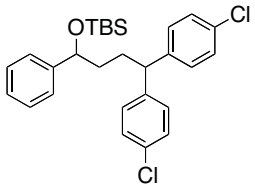
(4,4-*bis*(4-Fluorophenyl)-1-phenylbutoxy)(*tert*-butyl)dimethylsilane (**12**)



The same procedure used to synthesize **2** was used except 578 mg tributyl(4-fluorophenyl)stannane (1.50 mmol) was added, and the product was purified after 48 h by silica gel chromatography by eluting with hexanes. Yield: 66% (150 mg). The reaction to reproduce this yield was performed using 121 mg *tert*-butyldimethyl((1-phenylbut-3-en-1-yl)oxy)silane (0.46 mmol) with 532 mg of the arylstannane (1.38 mmol) and was

purified in the same way. Yield: 59% (123 mg); R_f = 0.74 w/ 20% acetone in hexanes. IR (neat) 3035, 2952, 2929, 2857, 1604, 1471, 1361, 1256, 1225, 1157, 1092, 979, 864, 835, 776, 700, 548 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ -0.16 (s, 3 H), 0.00 (s, 3 H), 0.88 (s, 9 H), 1.51-1.71 (m, 2 H), 1.89-2.12 (m, 2 H), 3.79 (dd, *J* = 8.0, 8.0 Hz, 1 H), 4.66 (dd, *J* = 5.2, 6.4 Hz, 1 H), 6.93 (t, *J* = 8.7 Hz, 4 H), 7.02 (d, *J* = 8.6 Hz, 2 H), 7.09 (d, *J* = 8.6 Hz, 2 H), 7.20-7.35 (m, 5H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ -4.7, -4.5, 18.4, 26.1, 31.6, 39.1, 49.8, 74.8, 115.4 (d, *J* = 21.2 Hz), 115.4 (d, *J* = 21.1 Hz), 126.0, 127.1, 128.2, 129.2 (d, *J* = 2.5 Hz), 129.3 (d, *J* = 3.0 Hz), 140.7 (d, *J* = 3.0 Hz), 140.8 (d, *J* = 2.5 Hz), 145.4, 161.5 (d, *J* = 244.2 Hz). HRMS $C_{28}H_{34}F_2OSi$ $(M+Ag)^+$ calcd.; 559.1398 obsd.: 559.1406.

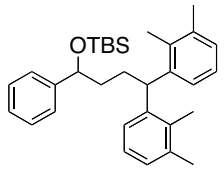
(4,4-*bis*(4-Chlorophenyl)-1-phenylbutoxy)(*tert*-butyl)dimethylsilane (**13**)



The same procedure used to synthesize **2** was used except 602 mg tributyl(4-chlorophenyl)stannane (1.50 mmol) was added, and the product was purified after 48 h by silica gel chromatography by eluting with hexanes. Yield: 45% (109 mg). The reaction to reproduce this yield was performed using 110 mg *tert*-butyldimethyl((1-phenylbut-3-en-1-yl)oxy)silane (0.42 mmol) with 505 mg of the arylstannane (1.28 mmol) and was purified in the same way. Yield: 46% (93 mg); R_f = 0.56 w/ 5% acetone, 5% benzene in hexanes. IR (neat) 3027, 2952, 2928, 2884, 2856, 1491, 1471, 1462, 1389, 1361, 1256, 1206, 1014, 978, 836, 775, 700, 546 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ -0.16 (s, 3 H), 0.01 (s, 3 H), 0.89 (s, 9 H), 1.51-1.71 (m, 2 H), 1.89-2.13 (m, 2 H), 3.78

(dd, *J* = 7.7, 7.7 Hz, 1 H), 4.66 (dd, *J* = 5.0, 6.6 Hz, 1 H), 7.05 (d, *J* = 8.7 Hz, 4 H), 7.20-7.31 (m, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ -4.7, -4.4, 18.4, 26.1, 31.2, 39.0, 50.5, 74.8, 126.0, 127.2, 128.3, 128.8, 138.8, 129.3, 129.3, 132.2, 143.2, 143.3, 145.3. HRMS $C_{28}H_{34}Cl_2OSi$ $(M+Ag)^+$ calcd.; 591.0807 obsd.; 591.0818.

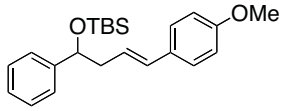
(4,4-*bis*(2,3-Dimethylphenyl)-1-phenylbutoxy)(*tert*-butyl)dimethylsilane (**15**)



The same procedure used to synthesize **2** was used except 593 mg tributyl(2,3-dimethylphenyl)stannane (1.50 mmol) was added, and the product was purified after 72 h by silica gel chromatography by eluting with hexanes. Sixty two mg (47%) of the starting alkene was recovered each experiment. Yield: 24-27% (65 mg and 57 mg); R_f = 0.57 w/ 10% EtOAc in hexanes. IR (neat) 3064, 3026, 2951, 2928, 2856, 1585, 1493, 1471, 1461, 1386, 1361, 1255, 1094, 1071, 1027, 1006, 977, 837, 776, 745, 724, 700, 548 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ -0.17 (s, 3 H), 0.00 (s, 3 H), 0.89 (s, 9 H), 1.70-1.90 (m, 4 H), 2.06 (s, 3 H), 2.10 (s, 3 H), 2.24 (s, 3 H), 2.25 (s, 3 H), 4.23 (dd, *J* = 7.4, 7.4 Hz, 1 H), 4.67 (dd, *J* = 5.0, 5.0 Hz, 1 H), 6.81-6.87 (m, 2 H), 6.96-6.99 (m, 4 H), 7.20-7.27 (m, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ -4.7, -4.5, 15.0, 18.4, 21.3, 26.1, 30.8, 39.5, 43.7, 75.0, 125.3, 125.3, 125.4, 126.2, 127.0, 127.7, 127.7, 128.1, 134.8, 134.9, 136.8, 142.9, 142.9, 145.4. HRMS $C_{32}H_{44}OSi$ $(M+Ag)^+$ calcd.; 579.2212 obsd.; 579.2230.

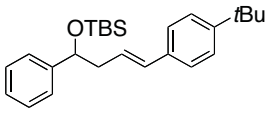
Isolation of Heck products shown in Figure 1.12

(*E*)-*tert*-Butyl((4-(4-methoxyphenyl)-1-phenylbut-3-en-1-yl)oxy)dimethylsilane



Isolated as a side product from the reaction used to synthesize **2**. Material was a mixture of the title compound and an isomer. Yield: 10-16% (18 mg and 30 mg); R_f = 0.71 w/ 10% EtOAc in hexanes. IR (neat) 3031, 2954, 2928, 2856, 1608, 1540, 1511, 1471, 1464, 1362, 1293, 1249, 1174, 1091, 1039, 1005, 966, 939, 837, 776, 753, 700, 668 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ -0.16 (s, 0.35 H), -0.12 (s, 3 H), 0.01 (s, 3 H), 0.05 (s, 0.24 H), 0.91 (s, 1 H), 0.88 (s, 9 H), 2.48-2.57 (m, 2 H), 3.31 (br d, *J* = 6.6 Hz, 0.31 H), 3.80 (s, 3 H), 4.72 (dd, *J* = 5.1, 7.2 Hz, 1 H), 5.17 (d, *J* = 6 Hz, 0.25 H), 6.05 (dt, *J* = 15.8, 7.2 Hz, 1 H), 6.32 (d, *J* = 15.8 Hz, 1 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 7.04-7.09 (m, 0.66 H) 7.23-7.33 (m, 7 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ -4.7, -4.6, 18.5, 26.0, 26.1, 27.7, 29.9, 35.1, 37.8, 40.7, 44.9, 55.5, 75.1, 75.6, 75.5, 113.8, 114.0, 114.1, 125.2, 126.0, 126.1, 127.0, 127.1, 127.3, 128.2, 128.2, 128.3, 129.4, 129.7, 130.8, 131.6, 135.1, 145.5, 158.9. HRMS $C_{23}H_{32}O_2Si$ $(M+Ag)^+$ calcd.; 475.1223 obsd.; 475.1212.

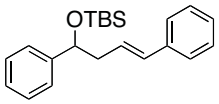
(*E*)-*tert*-Butyl((4-(4-(*tert*-butyl)phenyl)-1-phenylbut-3-en-1-yl)oxy)dimethylsilane



Isolated as a side product from the reaction used to synthesize **10**. Yield: 11-14% (22 mg and 27 mg); R_f = 0.84 w/ 5% EtOAc in hexanes. IR (neat) 3028, 2956, 2928, 2902, 2856, 1514, 1493, 1471, 1462, 1363, 1256, 1202, 1090, 1069, 1005, 967, 939, 836,

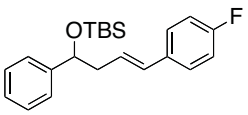
806, 776, 700, 556 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ -0.12 (s, 3 H), 0.03 (s, 3 H), 0.90 (s, 9 H), 1.30 (s, 9 H), 2.50-2.61 (m, 2 H), 4.73 (dd, *J* = 5.1, 7.2 Hz, 1 H), 6.16 (dt, *J* = 15.8, 7.2 Hz, 1 H), 6.36 (d, *J* = 15.9 Hz, 1 H), 7.23-7.32 (m, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ -4.6, -4.5, 18.5, 26.1, 31.5, 31.6, 45.0, 75.5, 125.6, 125.9, 126.1, 126.5, 127.2, 128.2, 132.0, 135.2, 145.4, 150.8. HRMS $C_{26}H_{38}OSi$ $(M+Ag)^+$ calcd.; 501.1743 obsd.; 501.1758.

(*E*)-*tert*-Butyl((1,4-diphenylbut-3-en-1-yl)oxy)dimethylsilane



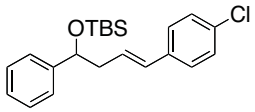
Isolated as a side product from the reaction used to synthesize **11**. Yield: 7-11% (12 mg and 18 mg); R_f = 0.16 w/ hexanes. IR (neat) 3061, 3027, 2954, 2928, 2894, 2855, 1734, 1700, 1653, 1599, 1540, 1521, 1506, 1494, 1472, 1437, 1362, 1256, 1215, 1086, 1070, 1005, 836, 776, 743, 699, 540 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ -0.12 (s, 3 H), 0.02 (s, 3 H), 0.88 (s, 9 H), 2.51-2.59 (m, 2 H), 4.74 (dd, *J* = 5.0, 7.4 Hz, 1 H), 6.21 (dt, *J* = 15.9, 7.2 Hz, 1 H), 6.38 (d, *J* = 15.9 Hz, 1 H), 7.19-7.33 (m, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ -4.7, -4.5, 18.5, 26.0, 45.0, 75.4, 126.0, 126.2, 127.1, 127.2, 127.4, 128.3, 128.7, 132.3, 137.9, 145.4. HRMS $C_{22}H_{30}OSi$ $(M+Ag)^+$ calcd.; 445.1117 obsd.; 445.1124.

(*E*)-*tert*-Butyl((4-(4-fluorophenyl)-1-phenylbut-3-en-1-yl)oxy)dimethylsilane



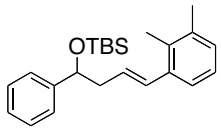
Isolated as a side product from the reaction used to synthesize **12**. Yield: 15-19% (26 mg and 34 mg); R_f = 0.78 w/ 20% acetone in hexanes. IR (neat) 3030, 2954, 2928, 2856, 1653, 1602, 1508, 1471, 1463, 1362, 1256, 1230, 1157, 1090, 1005, 966, 939, 810, 796, 776, 700, 569 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ -0.13 (s, 3 H), 0.01 (s, 3 H), 0.88 (s, 9 H), 2.50-2.60 (m, 2 H), 4.73 (dd, *J* = 5.0, 7.4 Hz, 1 H), 6.11 (dt, *J* = 15.9, 7.1 Hz, 1 H), 6.33 (d, *J* = 15.9 Hz, 1 H), 6.97 (t, *J* = 8.9 Hz, 2 H), 7.22-7.33 (m, 7 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ -4.7, -4.5, 18.4, 26.0, 44.9, 75.3, 115.6 (d, *J* = 21.7 Hz), 126.0, 127.1, 127.1, 127.2, 127.6 (d, *J* = 8.1 Hz), 128.3, 131.1, 134.1 (d, *J* = 3.5 Hz), 145.3, 162.2 (d, *J* = 245.6 Hz). HRMS $C_{22}H_{29}FOSi$ $(M+Ag)^+$ calcd.; 463.1023 obsd.; 463.1032.

(*E*)-*tert*-Butyl((4-(4-chlorophenyl)-1-phenylbut-3-en-1-yl)oxy)dimethylsilane



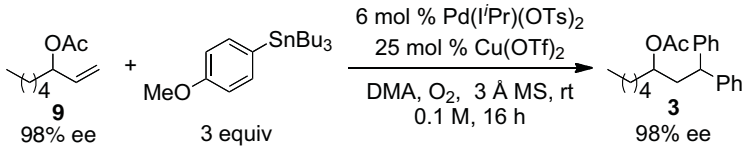
Isolated as a side product from the reaction used to synthesize **13**. Yield: 31-34% (58 mg and 63 mg); R_f = 0.68 w/ 5% acetone, 5% benzene in hexanes. IR (neat) 3028, 2954, 2928, 2895, 2856, 1491, 1471, 1462, 1453, 1404, 1388, 1361, 1256, 1091, 1068, 1012, 966, 938, 836, 776, 700, 548 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ -0.13 (s, 3 H), 0.00 (s, 3 H), 0.88 (s, 9 H), 2.50-2.60 (m, 2 H), 4.74 (dd, *J* = 5.0, 7.3 Hz, 1 H), 6.17 (dt, *J* = 15.9, 7.2 Hz, 1 H), 6.33 (d, *J* = 15.9 Hz, 1 H), 7.32 (d, *J* = 4.4 Hz, 4 H), 7.20-7.27 (m, 5 H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ -4.7, -4.4, 18.4, 26.0, 44.9, 75.3, 126.0, 127.3, 127.4, 128.1, 128.3, 128.8, 131.2, 132.7, 136.5, 145.2. HRMS $C_{22}H_{29}FOSi$ $(M+Ag)^+$ calcd.; 479.0727 obsd.; 479.0747.

(*E*)-*tert*-Butyl((4-(2,3-dimethylphenyl)-1-phenylbut-3-en-1-yl)oxy)dimethylsilane

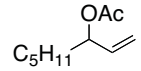
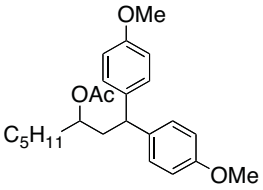


Isolated as a side product from the reaction used to synthesize **15**. Yield: 23-28% (43 mg and 52 mg); R_f = 0.63 w/ 10% EtOAc in hexanes. IR (neat) 3027, 2954, 2928, 2895, 2856, 1653, 1559, 1506, 1491, 1471, 1387, 1362, 1256, 1091, 1068, 1005, 969, 940, 854, 775, 699, 668 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ -0.12 (s, 3 H), 0.04 (s, 3 H), 0.88 (s, 9 H), 2.15 (s, 3 H), 2.27 (s, 3 H), 2.55-2.62 (m, 2 H), 4.77 (dd, *J* = 5.6, 5.6 Hz, 1 H), 5.96 (dt, *J* = 15.6, 7.1 Hz, 1 H), 6.58 (d, *J* = 15.6 Hz, 1 H), 7.03 (d, *J* = 5.1 Hz, 2 H) 7.17-7.34 (m, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ -4.6, -4.5, 15.5, 18.4, 20.8, 26.1, 45.2, 75.4, 124.2, 125.6, 126.1, 127.1, 128.2, 128.7, 128.8, 131.3, 133.9, 136.8, 137.5, 145.3. HRMS $C_{24}H_{34}OSi$ $(M+Ag)^+$ calcd.; 473.1430 obsd.; 473.1436.

Evaluation of enantiomeric excess retention



The same procedure used to synthesize racemic **3** was used except 24 mg (*S*)-oct-1-en-3-yl acetate (**9**) (0.14 mmol) was added, and the product was purified after 16 h by silica gel chromatography by eluting with 4% EtOAc in hexanes. The purified product was evaluated for enantiomeric excess using chiral SFC (see below).

compound	method	retention times (min)
	GC hold 100 °C 25 min	6.5 and 6.9 min
	SFC 5% MeOH 1.5 mL/min	5.5 and 6.1 min

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CHAPTER 2

DEVELOPMENT AND EVALUATION OF AN (*E*)-STYRENYL-SELECTIVE OXIDATIVE HECK REACTION

Introduction

The transition-metal catalyzed substitution of a vinylic carbon-hydrogen bond for a carbon-carbon bond, known as the Heck reaction,[1-4] has found utility in countless target-directed syntheses,[5-7] and has inspired the development of creative new methods[8,9] such as that described in Chapter 1.[10] The importance of this transformation has been highlighted by the 2010 Nobel committee's recognition, as R. F. Heck shared the prize in chemistry with E. Negishi and A. Suzuki. By far the most studied and utilized transition metal for these transformations has been palladium, although other metals are known to catalyze the reaction (vide infra). The classical Heck reaction, wherein the catalytic cycle[11] is initiated by Pd^0, utilizes vinyl or aryl oxidants, typically organic halides or pseudohalides such as organotriflates. In contrast, the mechanism of the palladium-catalyzed oxidative Heck reaction[12] is initiated by a transmetallation of an organometalic reagent with Pd^{II}. In both cases an sp^2 hybridized carbon bound to a Pd^{II} species 2.1). The newly functionalized carbon-carbon bond rotates so that the metal center is in a undergoes *syn*-carbopalladation with an olefin to give a Pd^{II}-σ-alkyl intermediate (Figure 2.1). The newly functionalized carbon-carbon bond rotates so that the metal center is in a

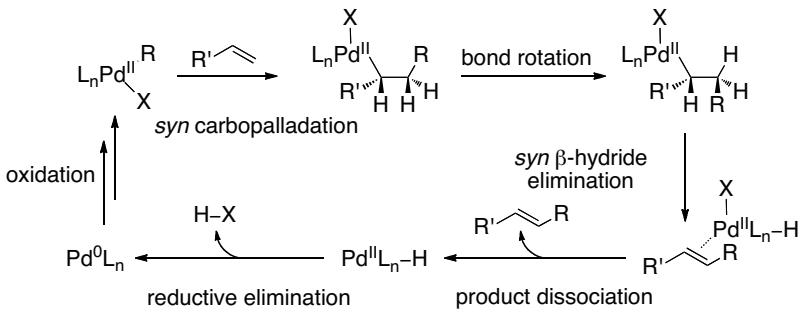


Figure 2.1. Generalized catalytic cycle for Heck reactions.

syn relationship with an adjacent hydrogen atom, which undergoes β-hydride elimination. The product then dissociates, liberating a Pd^{II}-hydride species, which undergoes reductive elimination to deliver palladium in the zero oxidation state. Oxidation, either by an organic molecule (classical Heck) or by an external oxidant (oxidative Heck), then permits the active catalyst to initiate another cycle.

While this transformation has proven indispensible to synthetic organic chemists, its efficient employment is limited in application to electronically polarized olefins. This includes, most frequently, alkenes bearing electron-withdrawing groups, and less commonly, those bearing electron-donating groups.[11] In the absence of substrate electronic bias, the carbopalladation step is not regioselective,[13] resulting in the formation of a mixture of intermediates, **A** and **B**, bearing a single new carbon-carbon bond at either of the two olefinic carbons (Figure 2.2). The intermediate bearing palladium at the terminal carbon, **B**, undergoes β-hydride elimination to deliver a terminal alkene product, but the intermediate bearing the metal center at the internal carbon, **A**, has multiple inequivalent hydrogens in β positions. In the absence of electronic bias, intermediates of this type undergo β-hydride elimination indiscriminately[4] with either a hydrogen atom at the benzylic (H_S leading to styrenyl products), or at the allylic (H_A leading to allylic

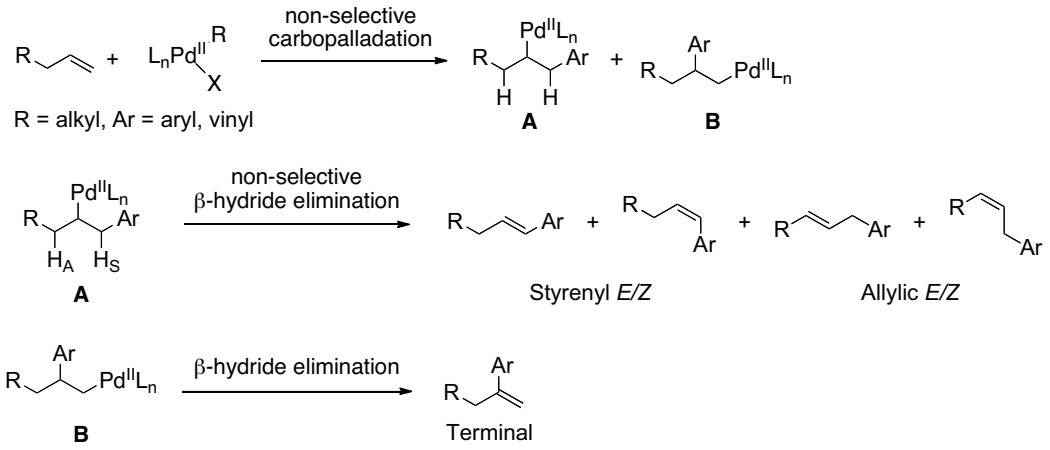


Figure 2.2. Isomeric products formed from Heck reactions performed on electronically nonbiased olefins.

products) position, leading to isomeric products. Additional isomeric products are formed if the Pd^{II}–H species continue to engage the resultant alkene, leading to products bearing olefins distal to the site of functionalization. Mixtures of (*E*)- and (*Z*)-olefin isomers can also result from Heck reactions, although this is generally a minor problem provided that the olefin substrate bears a group with at least moderate steric bulk. The result of such nonselective migratory insertion and β-hydride elimination is a complex mixture of newly-functionalized products bearing carbon-carbon bonds and olefins in multiple positions, and these products are typically inseparable.

A specific example of this lack of selectivity was provided by Heck, wherein the palladium-catalyzed reaction of bromobenzene with 1-hexene gave a mixture described as "phenylhexenes."[4] Since this initial observation that electronically nonbiased olefins perform poorly in the Heck reaction, very few reports describe the use of this class of alkenes, due to the fact that these substrates lead to complex product mixtures. Addressing this problem would significantly enhance the synthetic utility of this reaction,

and the discovery of a catalytic system which achieves this goal is the topic of this chapter.

Background

Oxidative Heck reactions using traditional substrates

Heck (and most subsequent researchers) focused on electron-deficient monosubstituted alkene substrates, where the new carbon-carbon bond forms at the terminal position of the alkene (vide infra). Electron-rich olefins, biased by the presence of a Lewis basic heteroatom, may also perform well in Heck reactions (vide infra). However, the use of these reactants results in a reversal of migratory insertion regioselectivity; the arene prefers to add to the internal carbon. There has been considerable debate[14-23] regarding the mechanistic rationale for the origin of selectivity in the migratory insertion step of the Heck reaction, and most studies have focused on Pd^0-catalyzed reactions. The contention concerns whether the arene bound to palladium attacks the more electron-deficient carbon, or whether the olefin attacks the palladium from the more electron rich position. This assumes that the selectivity is governed by electronic factors, although it could also be influenced by the steric bulk of the substrate, or by ligand modulation.[11] However, from a practical standpoint, the aryl group is delivered predominantly to the carbon with less electron density, while the metal center goes to the more electron-rich carbon (Figure 2.3 a) when using terminal alkenes. For both electron-rich and electron-deficient alkenes, β-hydride elimination obeys the Curtin Hammett principle,[11,24] and the ratio of (*E*)- and (*Z*)-product olefin isomers is a function of the stability of transition states leading to these products. With even moderate steric

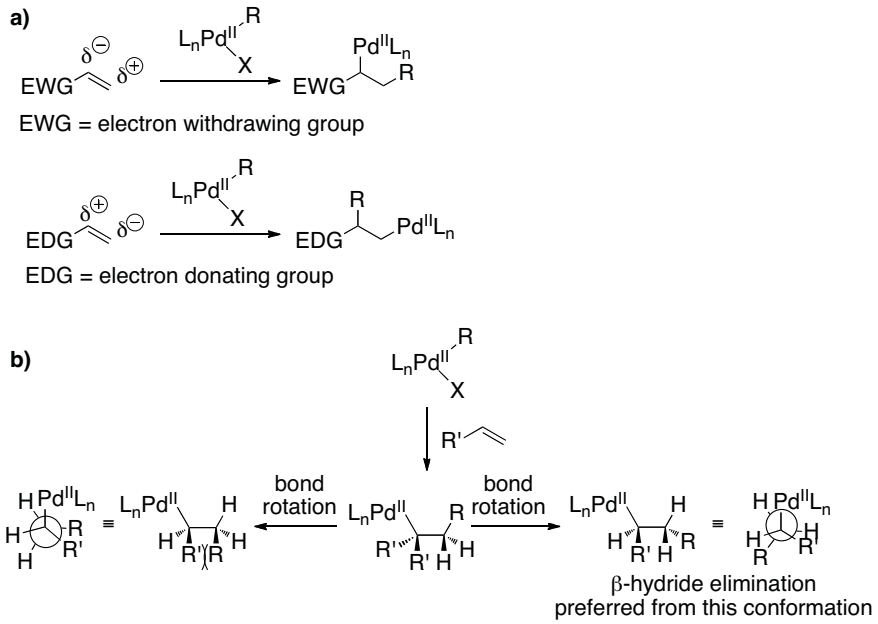


Figure 2.3. General guidelines for understanding the selectivity of **a)** migratory insertion and **b)** β-hydride elimination in Heck reactions.

bulk present on the olefin, this results in high selectivity for the (*E*)-alkene isomer (Figure 2.3 b). These general guidelines explain the selectivity observed in the examples to follow.

Although the majority of subsequent reports concerning the Heck reaction utilized organic oxidants, and are therefore examples of classical Heck reactions, the seminal report[1] employed organometallic reagents in the presence of stoichiometric amounts of group VIII metal salts. The majority of the entries in this initial report utilize Li_2PdCl_4 in combination with organomercury reagents as depicted in Figure 2.4 (note that the product is isolated as a methyl benzoate derivative due to the methanol solvent, not due as a result of transition metal catalysis). However, all group VIII metal salts, along with rhodium and ruthenium, tested gave at least trace amounts of product, and organolead and organostannanes, in addition to organomercury reagents, proved competent as sources of

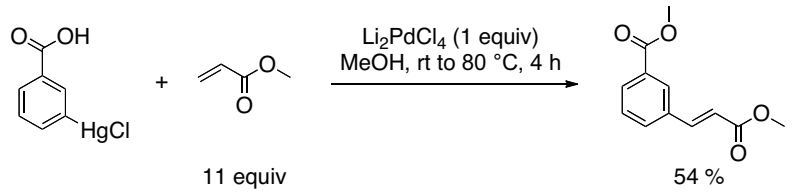


Figure 2.4. Seminal report of the oxidative Heck reaction.

the newly installed arene. Heck also reported that the reaction could be rendered catalytic in palladium by the addition of copper salts to the reaction mixture; a discovery analogous[25] to that reported by Smidt and coworkers in their study of the Wacker oxidation.[26] Interestingly, the larger synthetic community did not adopt this approach until decades later, instead focusing on what became known as classical Heck conditions (see Chapter 3).

In 1994 Uemura and coworkers reported the use of a more environmentally friendly (as compared to organo-lead, -mercury, and –tin reagents) source of the arene, namely arylboronic esters.[27] The group demonstrated that this variant of the Heck reaction could be performed using $Pd(OAc)_2$ in the presence of NaOAc at room temperature in acetic acid (Figure 2.5 a). The alkene scope included styrene derivatives and acrylates, and gave generally high yields and (*E*)-styrenyl selectivities. When disubstituted olefins were used, however, complex mixtures of mono- and di-arylated products were reported (Figure 2.5 b). The group proposed an unusual mechanism by which Pd^0 undergoes oxidative addition into the carbon-boron bond, but it is unclear whether this proposal is possible; the group does not report whether oxygen, which can reoxidize Pd^0 to Pd^{II}, was rigorously excluded from the reaction mixture. The group reports the formation of biphenyl as a side product (1–16% yield) of the reaction, which

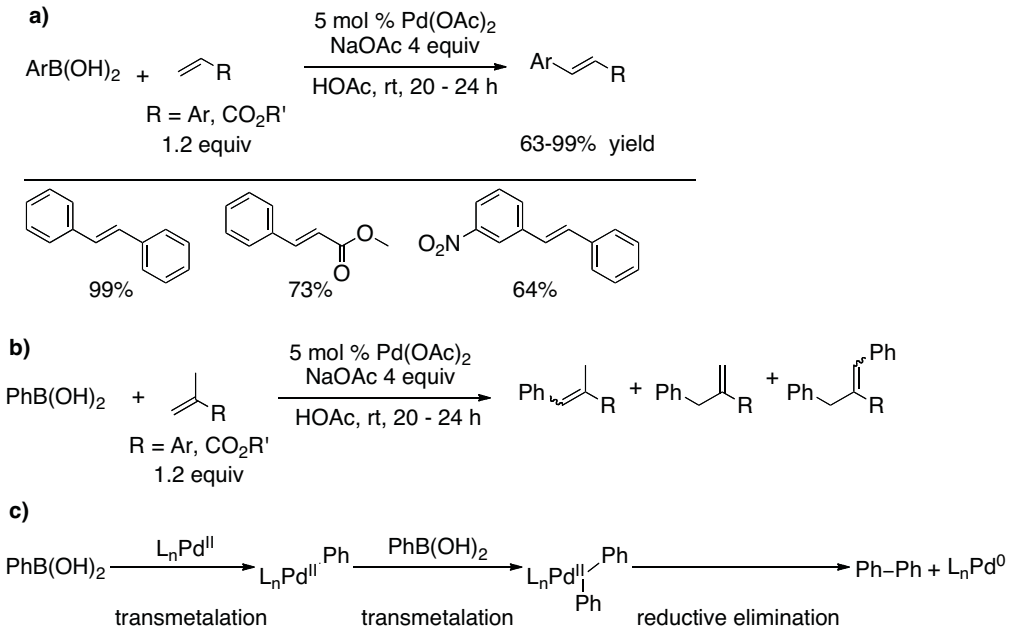


Figure 2.5. a) Cross-coupling of arylboronic acids with electronically biased olefins, and representative products**. b)** Poor selectivity when disubstituted olefins are used. **c)** Mechanism of biphenyl formation.

suggests that Pd^{II} catalysis does occur,[28] at least as a side reaction, under the reported conditions (Figure 2.5 c).

Mori and coworkers reported conditions,[12] which proceed by a more well-defined mechanism (Figure 2.6). The researchers note Heck's observation that the reaction could be rendered catalytic in palladium by the addition of copper salts, and propose transmetalation between the Pd^{II} species and $ArB(OH)_2$ rather than an oxidative addition into a carbon-boron bond. The scope of the reaction includes a variety of electronically-biased olefins, and the catalyst exhibits high selectivity for (*E*)-styrenyl products under these conditions. An exception to this high selectivity is observed when acrylonitrile is submitted, resulting in a product mixture containing 3:1 (*E*)*:*(*Z*) olefin isomers. This can be explained by the small nature of the nitrile group.

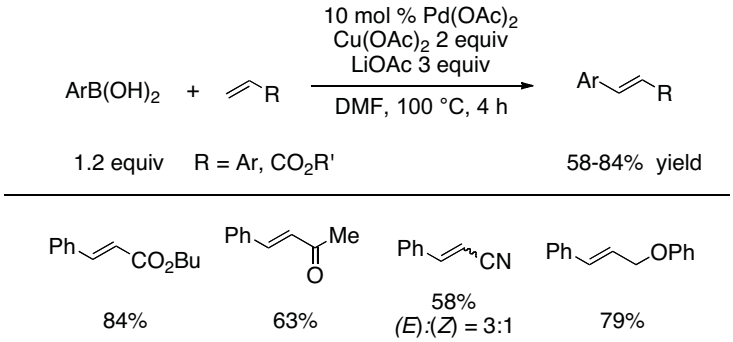


Figure 2.6. Mori and coworker's use of copper salts as oxidants in an oxidative Heck reaction, and representative products.

Jung and coworkers were able to demonstrate that oxygen is able to reoxidize Pd^0 to Pd^{II} in the context of a Heck-type cross coupling (Figure 2.7 a), and reported similar substrate scope to that reported previously.[29] The group also demonstrated that certain 1,2-disubstituted olefins gave single trisubstituted olefin products when submitted to these conditions, although several of the substrates of this type gave mixtures of product isomers (Figure 2.7 b).

The groups of Larhed[30,31] and Jung[32] each demonstrated the use of nitrogen-based ligands, specifically phenanthroline derivatives, in conjunction with molecular oxygen as the terminal oxidant in oxidative Heck reactions. (Figure 2.8). Each group noted benefits of employing these additives, although each referred to differing advantages. Larhed found that the use of 2,9-dimethyl-1,10-phenanthroline (dmphen) allowed the reaction to proceed to completion with the use of only 1 mol % $Pd(OAc)_2$, reduced from 10 % in the absence of this additive, using oxygen as the sole oxidant, and *N*-methyl morpholine (NMM) as base.[30] They later noted that the reaction could be effectively performed under an atmosphere of air, in the absence of base, and could be greatly accelerated by employing microwave heating.[31] Jung observed that the utilization of 1,10-phenanthroline (phen) suppressed homocoupling of the $PhB(OH)_2$ reagent and prevented

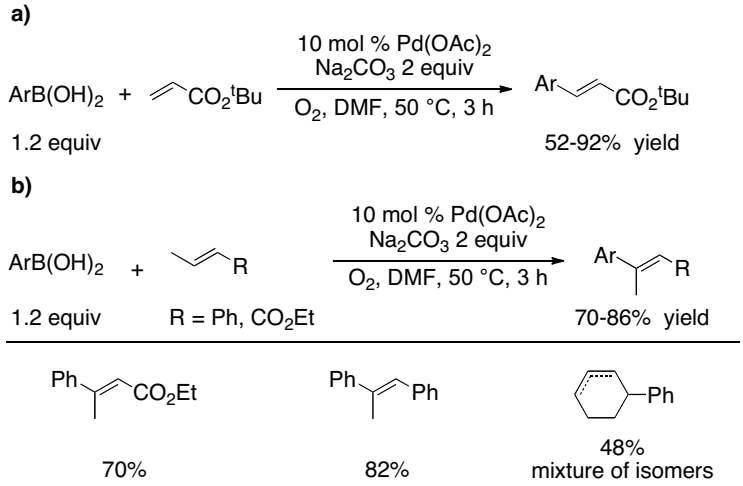


Figure 2.7. a) Oxidative Heck reaction using molecular oxygen as terminal oxidant. **b)** Use of disubstituted olefins as substrates in the oxidative Heck reaction.

the precipitation of the catalyst as palladium black. The reaction also proceeded at room temperature, and did not require added base (both DMF and the nitrogen-based ligand could act as base). Several other ligands proved effective as well, including 2,2'-bipyridine (bipy) and dmphen. The substrate scope of these reactions was very similar to that reported for the reactions described above.

While there are many other reports of oxidative Heck reactions using arylboronic acid derivatives, these are arguably the most attractive conditions, given the low catalyst loading, moderate temperatures, high yields, and discovery that added base may not be required. Provided the ease of handling organoboronic acid derivatives, and their low toxicity, these are also arguably the most attractive organometallic reagents, but it is important to note that several other classes of reagents have been utilized with success. It is also important to note that the conditions described above, and other catalytic systems reported for the cross coupling of olefins with organoboronic acid derivatives are *successful only with electronically biased olefins*.

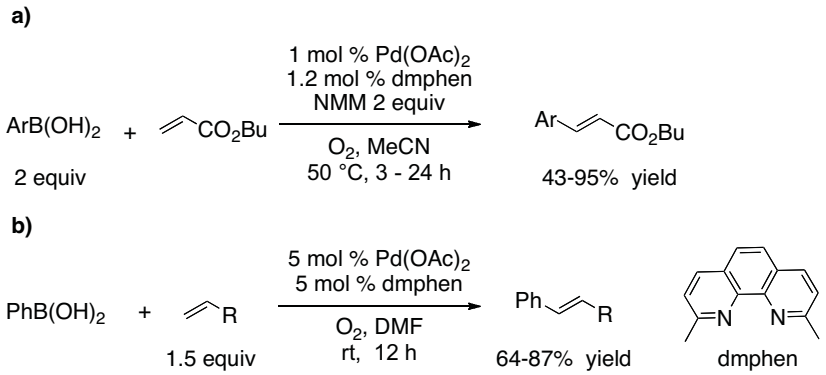


Figure 2.8. Oxidative Heck reactions utilizing nitrogenous ligands by the groups of **a)** Larhed, and **b)** Jung.

Aryltributylstannane reagents have been demonstrated to be similarly effective as organometallic reagents in oxidative Heck reactions by the groups of Mori[33] and Jung.[34] Similarly to the use of arylboronic acid derivatives, these reactions may also employ either copper salts or molecular oxygen as the terminal oxidant. Organosilicon reagents are also effective,[35,36] and there have been systems utilizing phenylantimony chloride,[37] and arylphosphonic acids.[38] Each of these reactions is demonstrated to perform well with electron-deficient olefin substrates.

As Heck observed in the seminal report,[1] several other transition metals are capable of catalyzing the oxidative Heck reaction, but most subsequent attention was directed to the use of palladium catalysis. In 2001, Lautens and coworkers reported success utilizing a rhodium catalyst to couple arylboronic acids and styrenes in aqueous solvent (Figure 2.9).[39] The reaction requires a phase transfer catalyst (SDS) to perform well, and interestingly, if styrene derivatives are replaced by vinyl-substituted nitrogen-based heteroaromatics, the products obtained are those from an addition-hydrolysis pathway, resulting in the formation of saturated stilbene products (Figure 2.9 b). Rhodium is also capable of cross coupling acrylate-type olefins and organosilanediols,[40]

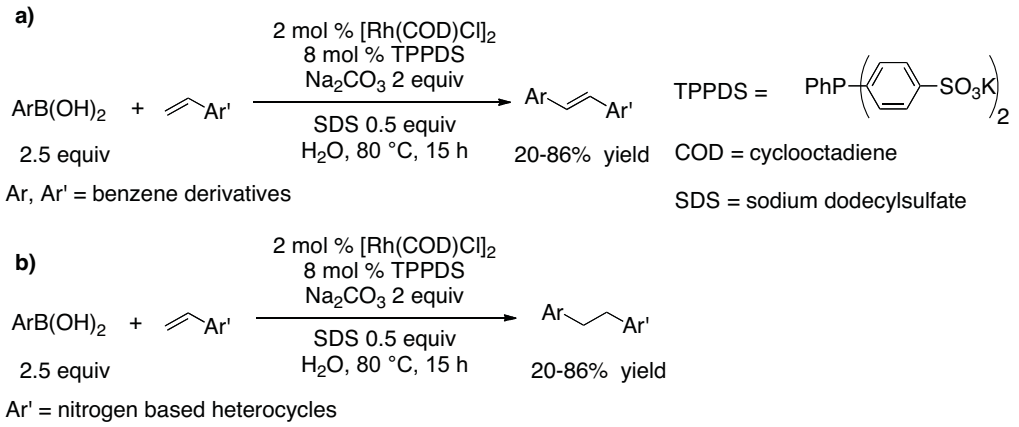


Figure 2.9. a) Rhodium catalyzed oxidative Heck reaction. **b)** Rhodium catalyzed addition-hydrolysis reaction using vinyl-substituted heterocycles as olefin substrates.

as demonstrated by Mori and coworkers. The substrate scope reported is rather limited, in terms of both olefins and arylsilanediols, and rhodium is an expensive catalyst, but the conditions are much simpler than those reported by Lautens.

Brown and coworkers demonstrated that butyl acrylate coupled with several arylboronic acids in the presence of catalytic amounts of a ruthenium complex in the presence of an amine base and copper acetate as terminal oxidant (Figure 2.10 a).[41] Very few examples of this reaction were provided, but this report represented an advancement, as previous reports employed stoichiometric ruthenium.[42,43] The use of catalytic amounts of an iridium complex has also been demonstrated to couple organometallic reagents, in this case organosilanes, with acrylates (Figure 2.10 b). Again, the substrate scope demonstrated was quite limited, and the Mori group reported only the use of electron-deficient alkenes.[44]

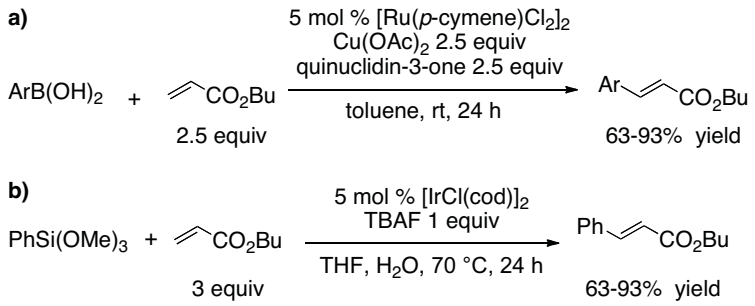


Figure 2.10. **a)** Ruthenium catalyzed oxidative Heck reactions reported by Brown. **b)** Iridium catalyzed oxidative Heck reactions reported by Mori.

Thus far the focus has been on olefin substrates that are electronically biased by virtue of bearing electron-withdrawing groups. However, alkenes bearing electron-donating heteroatoms also participate in oxidative Heck reactions, although their use is less common. Larhed and coworkers demonstrated the coupling vinyl alkyl ethers and enamides with arylboronic acids, reporting moderate to high regioselectivities.[45] In these cases, however, the arene preferentially adds to the internal carbon (vide supra), and the product (in the case of enol ethers) is hydrolyzed to give acetophenone derivatives (Figure 2.11). As the products of this reaction are 1,1-disubstituted olefins, the selectivity of the β-hydride elimination step is irrelevant.

Chelation-controlled oxidative Heck reactions

In all of the cases described above, alkenes with strong electronic bias were used in order to ensure high (*E*)-styrenyl selectivity. The regioselectivity of insertion was controlled by the electronic nature of the alkene, and the identity of the hydrogen atom to undergo β-hydride elimination, in most cases, was determined by the fact that only benzylic hydrogens were accessible. This clearly imposes a severe restriction on the types of products accessible from this reaction, and researchers have long been interested

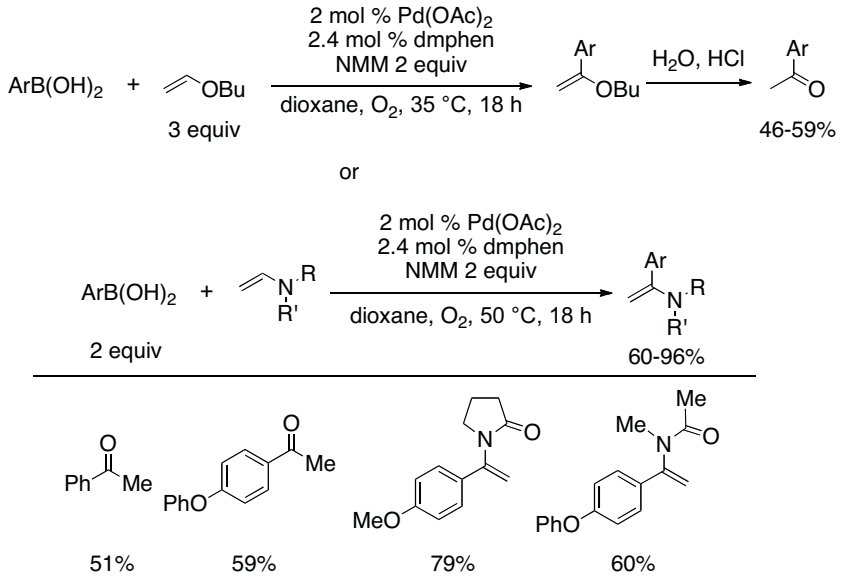


Figure 2.11. Larhed and coworker's use of electron rich alkenes, and representative products.

in overcoming this limitation. One recent strategy to overcome these restrictions has been to chelate the catalyst with proximal heteroatoms present in the alkene substrate. While several examples of this strategy have been published,[46-49] all but one operate under the classical, nonoxidative Heck mechanism, and will therefore be discussed in Chapter 3. The final example was published quite recently, and greatly expanded the potential applications of the oxidative Heck reaction.

White and coworkers initially discovered a one-pot reaction converting distally-, or nonfunctionalized alpha olefins to γ-acetoxy styrenes (Figure 2.12).[50] The reaction occurs in the presence of an exogenous carboxylic acid, utilizes benzoquinone as the terminal oxidant, and is catalyzed by a sulfoxide-ligated Pd^{II} catalyst. The second step of the reaction, following the addition of the acetoxy group, is an oxidative Heck reaction utilizing arylboronic acids. White and coworkers realized that the substrates successfully submitted to this reaction did not exhibit the degree of electronic bias typically associated

with successful oxidative Heck reactions. They hypothesized that chelation of the proximal heteroatom (represented by the acetate group) was likely responsible for the high degree of (*E*)-styrenyl selectivity observed in the reaction. If this was the case, the chelation-control strategy could represent a significant extension of substrates compatible with Heck chemistry.

The White group succeeded in the development of a chelation-controlled Heck reaction[51] using conditions similar to their difunctionalization reaction (Figure 2.13). The rationale behind the high selectivity observed when using these challenging substrates invokes coordination of the palladium catalyst to a heteroatom in the substrate, provided that this atom is in suitable proximity to form a 5- or 6-membered chelate. The incoming arene is directed to the terminal alkene carbon (Figure 2.14), rather than the internal carbon, by the coordinated heteroatom. Following insertion, the intermediate undergoes β-hydride elimination selectively with the benzylic hydrogen, because the palladacycle prevents the catalyst from engaging an allylic (endocyclic, labeled H_A) hydrogen atom. This metholology, however, also has limitations. If the selective delivery of the arene to the terminal carbon would require a chelate of seven carbons or more, or four carbons or less, the selectivity suffers drastically. This limitation is demonstrated in Figure 2.15, where substrates incapable of forming a 5- or 6-membered chelate deliver complex mixtures of products when subjected to the reaction. In summary, this methodology greatly expands the substrate scope of the oxidative Heck reaction. However, as it relies upon substrate chelation to deliver high selectivity for (*E*)-styrenyl products, it is still a

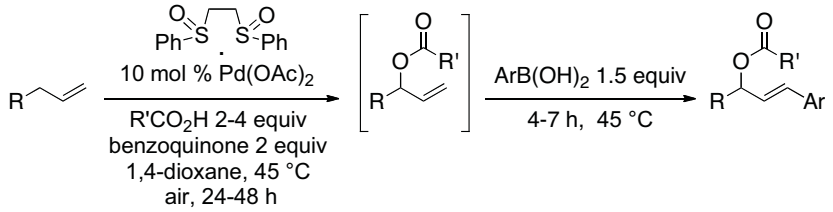


Figure 2.12. Conversion of electronically non-biased olefins to β-acetoxy styrenes.

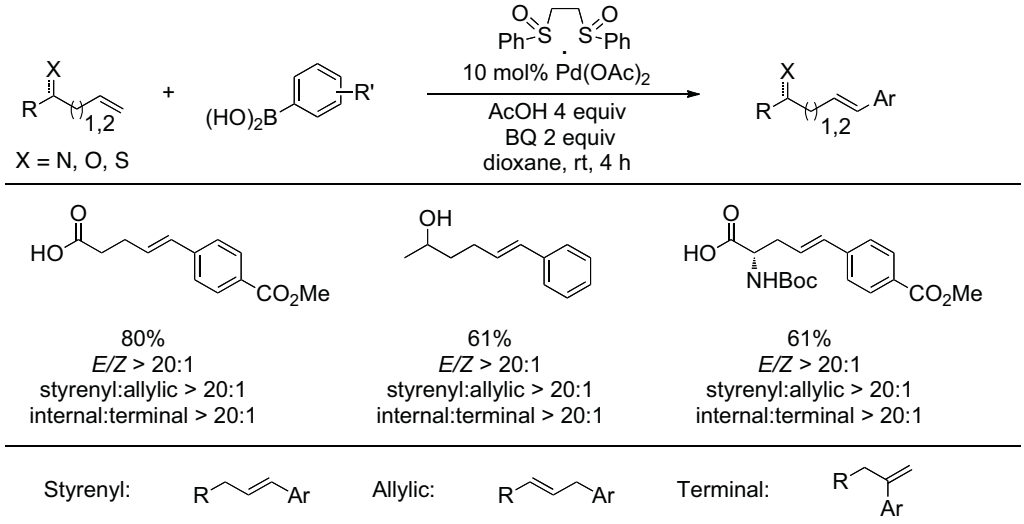


Figure 2.13. Chelation controlled oxidative Heck reaction reported by White and coworkers.

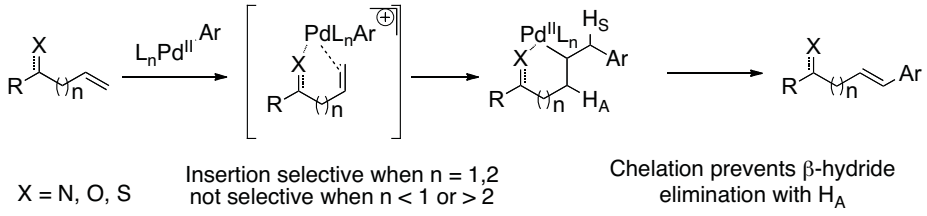


Figure 2.14. Mechanistic rationale for observed selectivity in White's chelation-controlled oxidative Heck reaction.

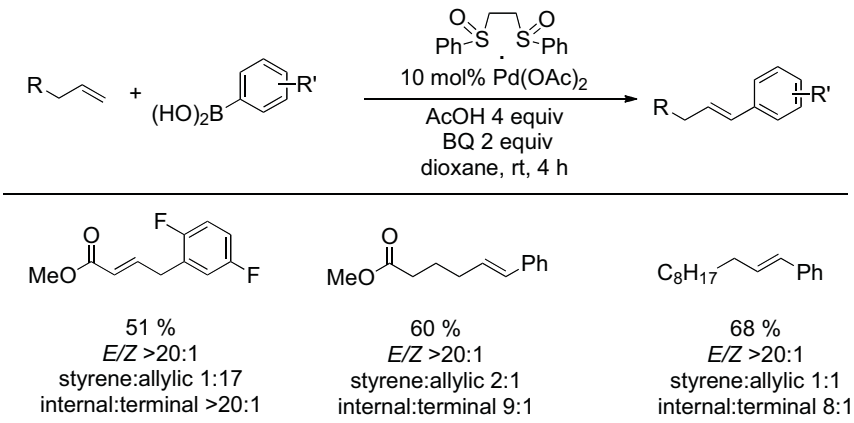


Figure 2.15. White's results using substrates incapable of forming a 5-, or 6-membered chelate.

substrate-controlled Heck reaction, as are those described above. Therefore, a reaction capable of delivering (*E*)-styrenyl products by catalyst-controlled migratory insertion and β-hydride elimination would further enhance the applicability of this important transformation.

Discovery and Optimization of a Catalyst-Controlled Oxidative Heck Reaction

As discussed in Chapter 1, an olefin diarylation reaction was developed, which utilizes the oxidative Heck mechanistic manifold, but intercepts reactive Pd^{II}-alkyl intermediates with an aryl stannane in a second transmetalation event to give products such as **2** from terminal alkenes like **1** (Figure 2.16).[10] The success of this system was partially attributed to the cationic nature of the catalyst, which was proposed to assist the catalyst in binding the olefin, preventing dissociation of a Heck product (see Chapter 1). Considering the ubiquitous nature of aryl boronic acid derivatives in cross coupling, these reagents were chosen for evaluation in the alkene difunctionalization reaction. As

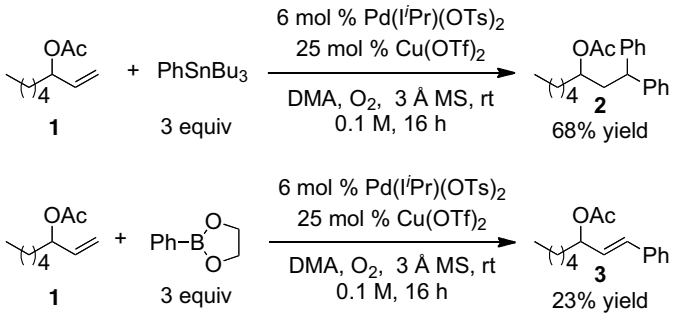
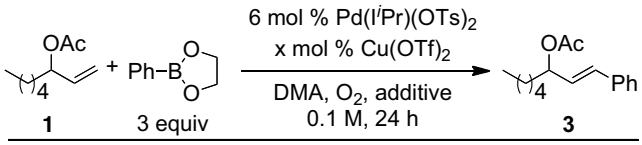


Figure 2.16. 1,1-Diarylation, and oxidative Heck reactions using **1**.

mentioned previously, the use of phenyl boronic ester in place of $PhSnBu_3$ resulted in only (*E*)-styrenyl Heck product **3** with no diarylation or isomeric products observed. This result represented a potentially significant advancement in the substrate scope of the Heck reaction, as the high selectivity observed did not appear to be dependent on substrate structure, in terms of either electronic bias or favorable chelation. The allylic alcohol derivative was chosen as a model substrate for optimization[52] due to the convenience of assaying the starting material, product, and product isomers by gas chromatography analysis, and because allyic acetates are known to participate in undesired side reactions under palladium catalysis.[53]

Optimization of this reaction was performed, wherein increasing the temperature to 40 ^oC resulted in improved yield of **3** without diminishing selectivity (Table 2.1, entry 2). Removing molecular sieves and decreasing the $Cu(OTf)_2$ loading further improved the GC yield to >99% in >20:1 selectivity for the (*E*)-styrenyl isomer (entries 3 and 4). It should be noted that the selectivity ratios reported refer to the ratio of the (*E*)-styrenyl product to the sum of all other isomeric products. As control experiments, the reaction was performed in the absence of the Pd^{II} catalyst, $Cu(OTf)_2$, or O_2, all of which resulted in little to no conversion of starting material (entries 5-7). Having identified optimal

Table 2.1. Optimization of the oxidative Heck reaction.



1 3 equiv **3**

entry	additive	temperature	x	% conversion[a]	% yield[a]
1	3 Å MS	rt	25	22	19
2	3 Å MS	40°C	25	>99	85
3	-	40°C	25	98	93
4	-	40°C	20	>99	>99
5[b]	-	40°C	20	<1	<1
6	-	40°C	0	64	12
7[c]	-	40°C	20	5	5

[a]Conversion and yield were calculated by comparing starting material and product peak integrations to the integration of an intern standard using GC analysis. [b]No Pd(I^{i}Pr)(OTs)$_2$ was used. [c]The reaction was run under nitrogen.

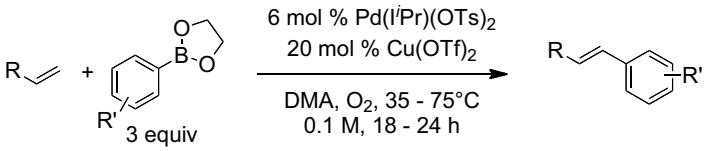
conditions, the reaction was scaled to 0.5 mmol to determine the isolated yield, and to confirm that the reaction performed similarly on larger scale. Submission of substrate **1**, which is susceptible to β-acetoxy elimination,[54] to the optimized reaction conditions on this larger scale resulted in 95% yield of the desired product (Table 2.2, entry 1).

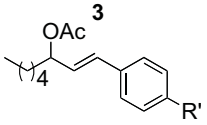
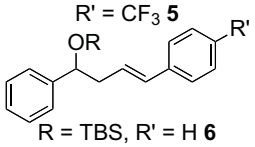
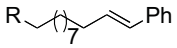
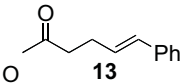
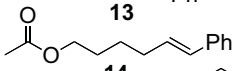
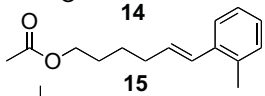
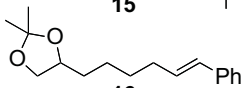
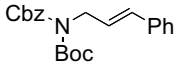
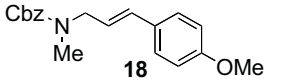
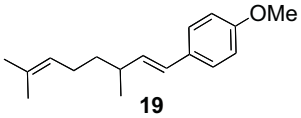
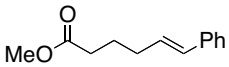
Scope Evaluation of the Oxidative Heck Reaction

Considering the unusual nature of the high selectivity observed, the scope of this transformation was evaluated. The reaction proved to be tolerant of a wide variety of functional groups commonly encountered in organic synthesis, delivering the desired (*E*)-styrenyl product in a >20:1 ratio in most cases (Table 2.2). Electron deficient arylboronic esters, including those bearing a methyl ester and a trifluoromethyl group, are highly effective (entries 2-3) when submitted to the reaction, delivering **4** and **5** in high selectivity. A substrate containing a TBS-protected homoallylic alcohol gives good yields

and high selectivities of products **6-9** using a range of arylboronic esters (entries 4-7), including those bearing electron-deficient, and electron-rich arene substituents. This was important to establish in terms of demonstrating the synthetic utility of this reaction; arene electronics appear not to affect the selectivity of the reaction when using terminal alkene substrates such as those shown in Table 2.2. A free homoallylic alcohol is also a compatible substrate delivering the desired product, **10**, in moderate yield (entry 8). It is interesting to note that free alcohols could potentially be oxidized under these conditions to carbonyl compounds,[55,56] but the products of this side reaction are not observed. Other functional groups on simple alkenes are well-tolerated, including a distal free primary alcohol (leading to product **11**), the corresponding chloride (product **12**), a ketone (entry 11) and an ester (entry 12). Use of a hindered aryl boronic ester requires increased catalyst loading and elevated temperatures, resulting in a reduction of selectivity (product **15**, 10:1 selectivity). An acetonide-protected diol is an excellent substrate despite the presence of Lewis acidic catalysts, which could engage this group in side reactions (entry 14). Nitrogen containing substrates were incompatible with previously reported reactions utilizing this catalyst,[9,10] but an allylic amine with two carbamate protecting groups performs well in the reaction delivering **17**. However, submission of a more electron rich carbamate leads to poor catalyst activity (entry 16), likely due to the more Lewis basic nitrogen coordinating to the catalyst and leading to deactivation. A substrate containing a trisubstituted olefin (entry 17) is a poor substrate under these conditions, giving only 30% yield of **19**. This is likely because the more electron-rich alkene binds to the catalyst, but does not react with it, preventing the desired reactivity. Finally, as a direct comparison to White's chelation-controlled oxidative Heck reaction, a substrate bearing a distal ester

Table 2.2. Scope of the oxidative Heck reaction.



entry	product	temperature	% yield[a]
1	**3** 	40	95
2	R' = C(O)OMe **4**	45	97
3	R' = CF_3 **5**	45	73
4	 R = TBS, R' = H **6**	35	81
5	R = TBS, R' = OMe **7**	35	80
6	R = TBS, R' = F **8**	45	87
7	R = TBS, R' = C(O)Me **9**	45	78
8	R = H, R' = H **10**	40	63[b]
9	 R = OH **11**	35	80[b]
10	R = Cl **12**	35	89
11	 **13**	35	69
12	 **14**	35	88[b]
13[b]	 **15**	75	81[b,c]
14	 **16**	35	89[b]
15	 **17**	40	89
16	 **18**	40	45[d]
17	 **19**	55	30[e,f]
18	 **20**	40	95[b]

[a]Yields are average of two experiments performed on 0.5 mmol scale. The selectivity for (*E*)-styrene > 20:1 unless otherwise noted. [b]The selectivity for (*E*)-styrene was 10:1. [c]Using 10 mol % Pd(I^{i}Pr)(OTs)$_2$. [d]Recoved 44% starting material. [e]Selectivity for (*E*)-styrene was 6:1. [f]The remainder of the mass balance for this reaction was mainly recovered starting material.

performed well in this reaction, delivering excellent yield and high selectivity for **20**. The use of this substrate under White's[51] conditions resulted in a 1.2:1 mixture of isomers, as determined by ^{1}H NMR integration. Of note, an enantiomerically-enriched sample of **1** was subjected to the reaction conditions (Figure 2.17) with no resulting erosion in enantiomeric excess, further demonstrating this reaction's potential utility in organic synthesis.

Unsuccessful Oxidative Heck Reactions

Several of the reactions performed in the scope evaluation failed completely, or gave such poor results that the products were not isolated. For example, heteroaromatic boronic esters, including pyrimidine, indole, and isooxazole arenes, appear to be incompatible with this reaction, resulting in no desired product. (Figure 2.18). A singly protected allylamine derivative gave only trace product, as did a tosyl-protected homoallylic amine, and a substrate bearing a phthalamide protected amine. A carboxylic acid-bearing substrate gave only trace product, as did a substrate bearing a nitrile. The incompatibility of these functional groups is likely due to their Lewis basic nature, which presumably deactivates the catalyst. For reasons that are poorly understood, submission of undecene resulted in complete conversion, but gave poor selectivity with the (*E*)-styrenyl product favored over all other isomers by only a 3:1 ratio.

In order to demonstrate that the high selectivity observed under these conditions is attributable to the Pd($I^{i}Pr$)$(OTs)_2$ catalyst, substrate **21**, which is highly susceptible to the formation of undesired isomeric products,[51] was submitted to similar conditions using

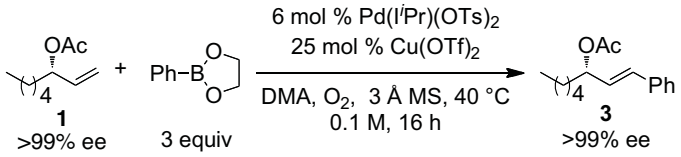


Figure 2.17. Retention of enantiomeric excess in the oxidative Heck reaction.

more traditional catalysis (Table 2.3). The reaction did not proceed when chloride was used as the counterion on palladium and copper (entry 1), while acetate was more effective, delivering the product in diminished selectivity in comparison with the cationic palladium system (entry 2 vs 6). Using $Pd(OAc)_2$ or $Pd(MeCN)_2(OTs)_2$ in conjunction with $Cu(OTf)_2$ resulted in the precipitation of Pd^0 (entries 3 and 4), and while the $[Pd(I^iPr)(Cl)_2]_2$ catalyst did not decompose in the presence of $Cu(OTf)_2$, the reaction proceeded more sluggishly (entries 5 vs 6). These results suggest that both a highly electrophilic palladium center and the stabilizing ligand are crucial for selective and high-yielding catalysis.

Mechanistic Analysis

In view of the unusually high selectivity observed in this oxidative Heck reaction, it was important to gain insight into the mechanistic origin of the selectivity. Specifically, it would be interesting to probe whether the hydrogen atom undergoing β-hydride elimination in the selectivity-determining step displayed protic, hydridic, or hydrogen-atom like character. Initial experiments designed to evaluate electronic effects upon product distribution focused on the submission of allyl benzene, **22**, to the oxidative Heck reaction, utilizing various electronically disparate arylboronic esters (Figure 2.19). However, assaying the data proved difficult, due to the similarity of the two products,

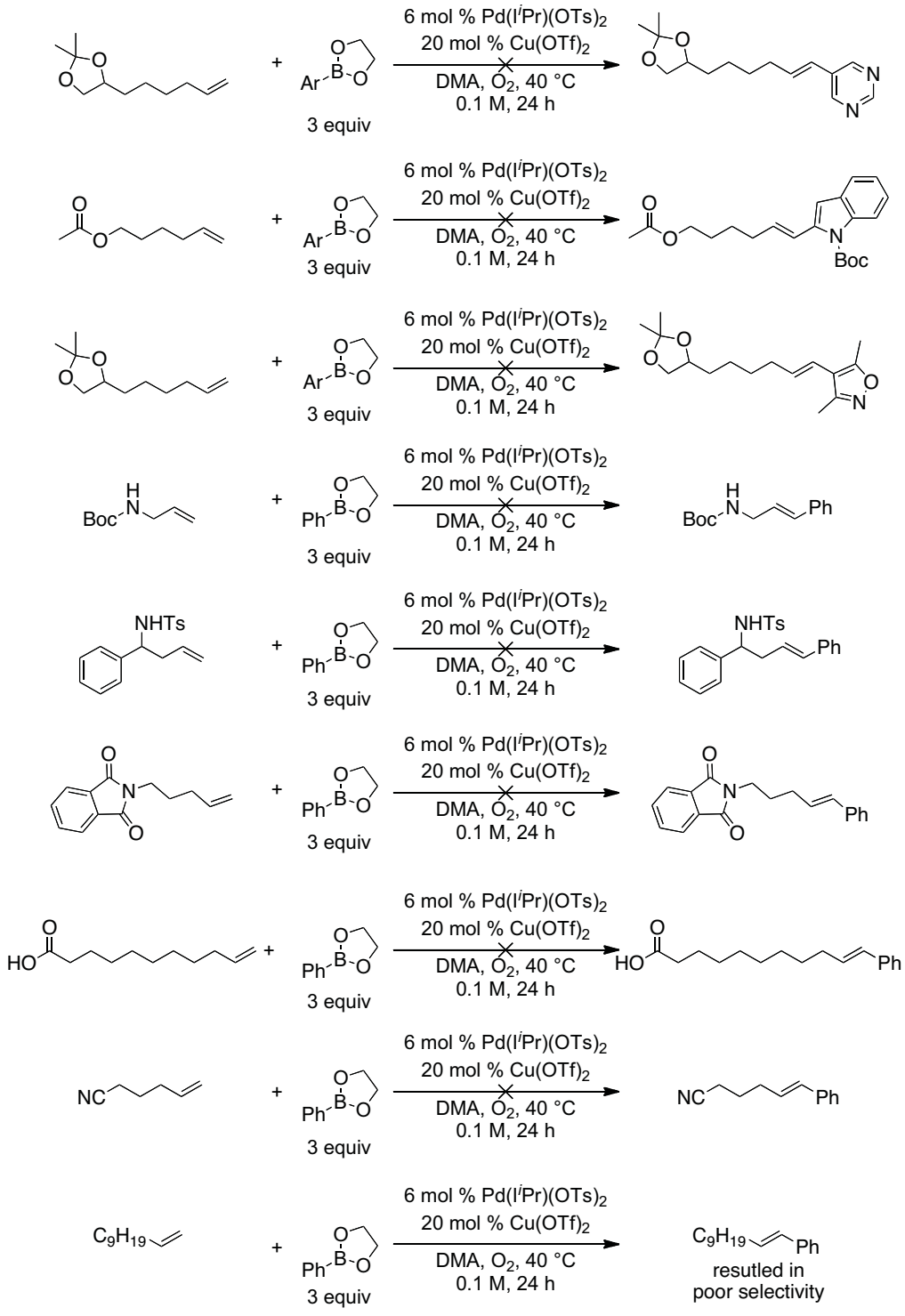
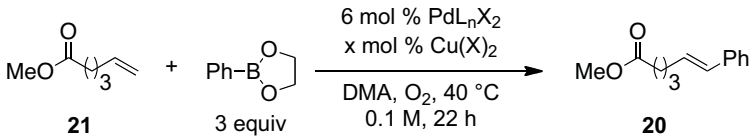


Figure 2.18. Desired products of failed, or poorly performing reactions.

Table 2.3. Use of common Pd^{II} salts in the oxidative Heck reaction.



21 **20**

entry	Pd^{II} source	Cu^{II} source	% conversion[a]	% yield[a]	selectivity[b]
1	$Pd(MeCN)_2Cl_2$	$CuCl_2$	15.3	<1	-
2	$Pd(OAc)_2$	$Cu(OAc)_2$	>99	35.3	6.2:1
3	$Pd(OAc)_2$	$Cu(OTf)_2$	>99	55.7	2.0:1
4	$Pd(MeCN)_2(OTs)_2$	$Cu(OTf)_2$	>99	99	3.4:1
5	$[Pd(I^iPr)Cl_2]_2$	$Cu(OTf)_2$	79.6	60.8	4.4:1
6	$Pd(I^iPr)(OTs)_2$	$Cu(OTf)_2$	>99	96.3	9.8:1

[a]Conversion and yield were calculated by comparing starting material and product peak integrations to the integration for an internal standard using GC analysis. [b]The selectivity is **20**:all other isomers, as determined by GC analysis.

$\mathbf{23_{Ar}}$ and $\mathbf{23_{Ph}}$, isolated from each reaction. Instead, β,γ-unsaturated ester **24** was subjected to the reaction conditions with electronically disparate arylboronic esters. This experiment probes the partitioning of intermediate **C** via β-hydride elimination of either H_A or H_S (Figure 2.20 a), and results in data easily characterized by ^{1}H NMR analysis (Figure 2.20 b). Plotting the log of the ratio of products $\mathbf{25_A}$ and $\mathbf{25_S}$ versus Hammett σ values for the corresponding aryl boronic ester substituent results in an unusual Hammett correlation wherein a break in linearity at σ = 0 (R = H) was revealed (Figure 2.20 c).[57,58] Typically, a Hammett correlation of this type is attributed to a change in reaction mechanism. According to this analysis, electron rich arenes favor the styrenyl product as compared to phenyl wherein the electron donor on the arene supports positive charge buildup resulting in a classic hydridic delivery of H_S to Pd. Surprisingly, electron poor arenes also favor the styrenyl product relative to phenyl. On the basis of a change-in-mechanism analysis, a possible explanation is that electron poor substituents are stabilizing a developing negative charge at the benzylic site implying that the loss of H_S

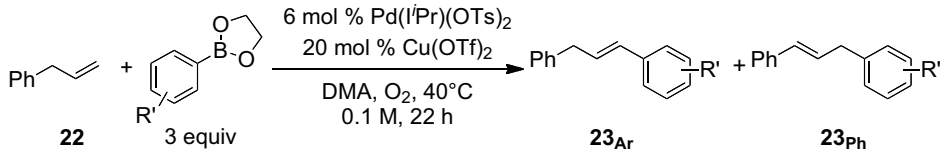
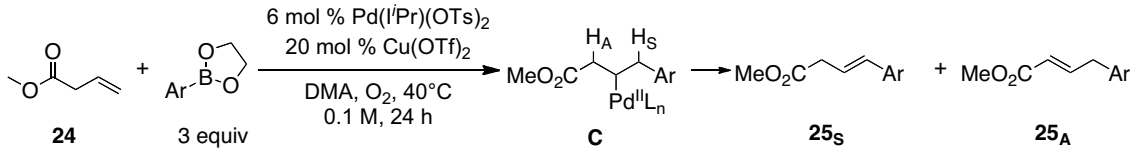


Figure 2.19. Attempted Hammett analysis of the catalyst-controlled oxidative Heck reaction using **22**.

is more protic in nature. However, if acidity dominates the product ratio, one would expect to observe the α,β-unsaturated ester as the sole observable product since the pK_a of protons α to esters (~25) is substantially lower than that of the toluene methyl group (~38). For this reason, if the "protic-hydrogen" mechanism were operative, one would expect to see the α,β-unsaturated ester product overwhelmingly favored. This was not observed, and the change-in-mechanism analysis was therefore ruled out.

Another possibility is that the palladium-hydride species may eliminate and reinsert repeatedly to arrive at equilibrium mixtures of product olefins. By this analysis, the ratios presented in Figure 2.19 are simply a product of equilibration. As part of the mechanistic analysis evaluating this oxidative Heck reaction mechanism as compared to reactions catalyzed by more traditional palladium salts, a similar product distribution series of experiments was conducted, utilizing $Pd(OAc)_2$ as catalyst (Figure 2.21). Under these conditions, product ratios were essentially unaffected by arene electronics, leading to mixtures of approximately 2:1 styrene:α,β-unsaturated ester regardless of the electronic nature of the arene. While this was not informative as to the factors dictating product ratios in traditional oxidative Heck chemistry, it did lead to samples of $\mathbf{25_A}$ + $\mathbf{25_S}$ in ratios not delivered by the catalyst-controlled oxidative Heck reaction. For example, the ratio of products **25** bearing 4–CF_3 substituents synthesized using $Pd(OAc)_2$ (2.4:1 $\mathbf{25_A}$:$\mathbf{25_S}$) was different from the ratio provided by the catalyst-controlled oxidative Heck

a)



b)

Ar	25$_A$/25$_S$	Ar	25$_A$/25$_S$
4-OMe	0.88	4-F	1.92
4-O*i*Pr	0.93	4-Cl	1.31
4-Me	1.34	4-CO$_2$Me	1.07
4-*i*Pr	2.04	4-COMe	1.05
4-*t*Bu	2.12	4-CF$_3$	0.69
4-H	2.92		

c)

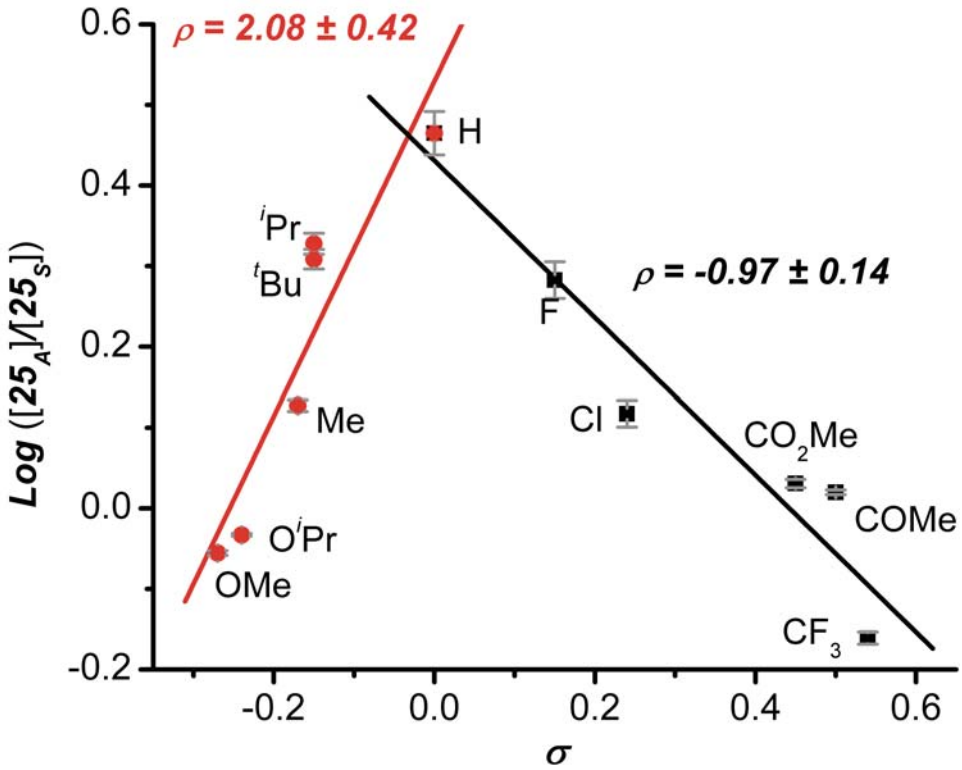
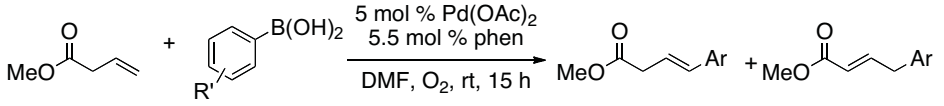


Figure 2.20. a) Product partitioning experiment using **24**. **b)** Resulting product ratios. **c)** Hammett plot analysis of the catalyst-controlled oxidative Heck reaction using β,γ-unsaturated ester **24**.



R	σ	Ratio $\mathbf{25_S}$:$\mathbf{25_A}$
Ar = 4-OMe	-0.27	1.9:1
Ar = 4-F	-0.17	1.9:1
Ar = 4-Me	+0.15	1.9:1
Ar = 4-OMe	+0.53	2.4:1

Figure 2.21. Product distribution of the oxidative Heck reaction using a traditional catalyst.

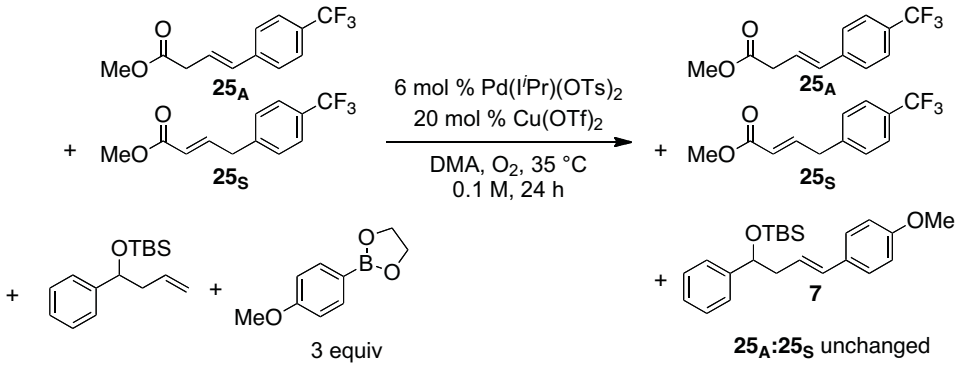


Figure 2.22. Crossover experiment suggesting that product ratios are not dictated by equilibration.

reaction (1.4:1 $\mathbf{25_A}$:$\mathbf{25_S}$). This permitted a preliminary evaluation of the equilibration hypothesis. The sample of $\mathbf{25_A}$ + $\mathbf{25_S}$ bearing 4–CF_3 groups prepared by traditional oxidative Heck catalysis was submitted to the catalyst-controlled oxidative Heck reaction to prepare **7** (Figure 2.22). The ratio of products was the same prior to submission to this reaction and after. Given that this sample was of a composition not delivered by the reaction developed in the Sigman laboratory, one would predict that the ratio may change over the course of the reaction to prepare **7**, if palladium-hydride species reinsert and eliminate to deliver equilibrated product ratios. The fact that this was not observed suggests that the catalyst-controlled oxidative Heck reaction is not selective for styrenes

simply by virtue of equilibrating to these products. However, it could also be the case that palladium-hydride species do not insert into disubstituted olefins, and the equilibration pathway to the observed product ratios cannot be fully ruled out at this time.

Another interesting possibility is that the strength of the C–H bond is dictating the product distribution in this reaction. Indeed, both electron-donating and electron-withdrawing substituents have been reported to stabilize radicals on toluene derivatives as compared to toluene itself.[59] The measurable observation under this type of mechanism would likely be a Hammett analysis resembling that in Figure 2.19. Analysis of the data in this fashion lead to the conclusion that relative C–H bond dissociation energy may dictate product distribution in this oxidative Heck variant (Figure 2.23). While this analysis is in the preliminary stages, the electrophilic nature of the catalyst coupled with the exceptional observed selectivity for benzylic C–H bond abstraction is suggestive of this hypothesis.

Alternative explanations could also be invoked, however. For example, the catalyst could coordinate with differential affinity to adjacent arenes with disparate electronic characteristics, perturbing the proximity of the two types of β-hydrogens and influencing product ratios. It is also possible that with the metal center bound to an alkyl chain, bond dissociation energies of adjacent C–H bonds are significantly different than would normally be expected. Possibilities such as these, and others, are difficult to rule out at this time. Future computational work may shed light on why a highly electrophilic catalyst appears to be more sensitive to the electronic natures of C–H bond undergoing β-hydride elimination than are more traditional catalysts, and whether the bond dissociation energy hypotheses outlined above is reasonable.

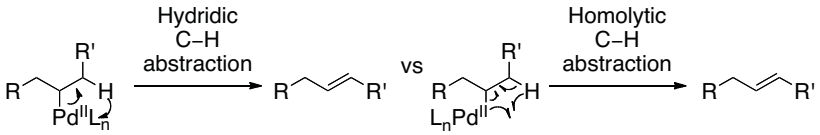


Figure 2.23: Hydride abstraction vs. C–H abstraction mechanisms of β-hydride elimination.

Conclusions

In conclusion, the Heck reaction provides an important tool to synthetic organic chemists, and provides mechanistic inspiration for the development of new methodology. For most of the long history of this reaction, it was limited to the use of electronically-biased alkene substrates. More recently, the oxidative Heck reaction was extended to the use of electronically non-biased olefins, but substrate-control using chelation is required to deliver high (*E*)-styrenyl selectivity. Based upon a serendipitous discovery when attempting to extend the scope of a 1,1-diarylation reaction of terminal olefins, it was discovered that an *N*-heterocyclic carbene-ligated electrophilic palladium catalyst is capable of distinguishing between benzylic and aliphatic β-hydrogens. This discovery was developed into the first catalyst-controlled oxidative Heck reaction capable of delivering (*E*)-styrenyl products in high yield and selectivity. The reaction is tolerant of a wide range of functional groups commonly encountered in organic synthesis, the conditions of the reaction are quite mild, and the reaction does not require added base. Preliminary mechanistic investigations suggest that both the cationic palladium center, and the stabilizing ligand are required to deliver the high selectivity observed. Further studies suggest that the catalyst distinguishes between beta hydrogens on the basis of C–H bond strength.

Experimental

General considerations

Dry dimethylacetamide (DMA) was purchased from Aldrich and stored over activated 3 Å molecular sieves (3 Å MS). 3 Å MS used in oxidative Heck reactions were powdered and activated by heating with a Bunsen burner while under vacuum. Terminal olefins were purchased from Aldrich or Acros, or synthesized according to the procedures referenced. Bu_3SnPh was purchased from Gelest Inc. Aryl boronic acids were purchased from Frontier Scientific. Palladium(II) chloride was purchased from Pressure Chemicals. (*S*)-1-Octene-3-ol was purchased from Fluka. $[Pd(allyl)Cl]_2$ and $[Pd(I^iPr)Cl_2]_2$[56] were synthesized according to literature procedures. ^{1}H-NMR spectra were obtained at 300 MHz or 400 MHz, chemical shifts are reported in ppm, and referenced to the $CHCl_3$ singlet at 7.26 ppm or to the center peak of the DMSO-D_6 quintet at 2.50 ppm. ^{13}C-NMR spectra were obtained at 75 MHz or 100 MHz and referenced to the center peak of the DMSO-D_6 septet at 39.51 ppm. The abbreviations s, d, t, quint, dd, ddd, dt, m stand for the resonance multiplicities singlet, doublet, triplet, quintet, doublet of doublets, doublet of doublets of doublets, doublet of triplets and multiplet, respectively. Thin-layer chromatography was performed with EMD silica gel 60 F254 plates eluting with solvents indicated, visualized by a 254 nm UV lamp and stained with potassium permanganate. Flash chromatography was performed using EM reagent silica 60 (230-400 mesh). IR spectra were recorded using a Thermo Nicolet FT-IR. HRMS data were obtained on a Waters LCP Premier XE instrument by ESI/TOF. Chiral GC (gas chromatography) analysis was performed using a Hewlett Packard HP 6890 Series CG system fitted with a HP-Chiral permethylated β-cyclodextrin column. SFC (supercritical

fluid chromatography) analysis was performed at 40 ºC, using a Thar instrument fitted with an AD-H column.

Procedure for the preparation of $Pd(I^iPr)(OTs)_2$

A vial was charged with 150 mg AgOTs (0.54 mmol, 6.0 equiv.) in a glove box in the dark. The vial was removed from the glove box, and immediately covered with aluminum foil. $[Pd(I^iPr)Cl_2]_2$ (100 mg, 0.09 mmol, 1 equiv.) was added, along with 5.0 mL technical grade dichloromethane, and a stir bar was added, with nitrogen flow into the vial. The mixture was stirred for 4 h prior to filtering through Celite with dichloromethane. The resulting solution was concentrated in vacuo at room temperature to 0.5 mL, and filtered through Celite with dichloromethane. The solution was then concentrated in vacuo at room temperature and stored under nitrogen to give $Pd(I^iPr)(OTs)_2$ in 95% yield (143 mg). It is essential that extreme care be used in the synthesis of this catalyst. Even minor impurities will result in significantly inferior results.

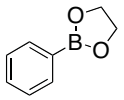
Synthesis of alkene substrates

Oct-1-en-3-yl acetate (**1**),[60] *tert*-butyldimethyl((1-phenylbut-3-en-1-yl)oxy) silane,[61] 1-phenylbut-3-en-1-ol,[61] 11-choroundec-1-ene,[62] 4-(hex-5-enyl)-2,2-dimethyl-1,3-dioxolane,[63] and benzyl allylmethyl carbamate[64] were prepared following literature procedures and purity confirmed via ^{1}H NMR. (*N*-Cbz-*N*-Boc) allylamine was prepared following the literature procedure,[65] and its purity confirmed by ^{1}H NMR.[66] (*S*)-1-Octene-

3-ol was converted to **1** using the same procedure as that used to synthesize racemic **1**. The enantiomeric excess of **3** was determined by chiral GC (see below).

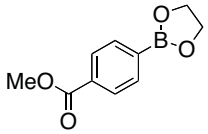
Synthesis of aryl boronic esters

2-Phenyl-1,3,2-dioxaborolane



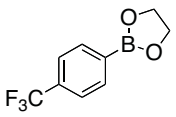
2-Phenyl-1,3,2-dioxaborolane was synthesized according to a previously reported procedure and the ^{1}H-NMR spectrum was compared to the previously reported spectrum.[67]

Methyl 4-(1,3,2-dioxaborolan-2-yl)benzoate



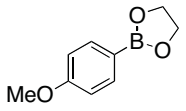
Methyl 4-(1,3,2-dioxaborolan-2-yl)benzoate was synthesized according to a previously reported procedure and the ^{1}H-NMR spectrum was compared to the previously reported spectrum.[67]

2-(4-(Trifluoromethyl)phenyl)-1,3,2-dioxaborolane



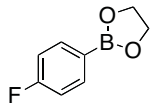
2-(4-(Trifluoromethyl)phenyl)-1,3,2-dioxaborolane was synthesized according to a previously reported procedure[67] and the ^{1}H-NMR spectrum was compared to the previously reported spectrum.[68]

2-(4-Methoxyphenyl)-1,3,2-dioxaborolane



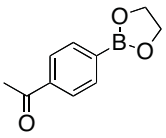
2-(4-Methoxyphenyl)-1,3,2-dioxaborolane was synthesized according to a previously reported procedure and the ^{1}H-NMR spectrum was compared to the previously reported spectrum.[67]

2-(4-Fluorophenyl)-1,3,2-dioxaborolane



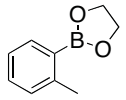
2-(4-Fluorophenyl)-1,3,2-dioxaborolane was synthesized according to a previously reported procedure and the ^{1}H-NMR spectrum was compared to the previously reported spectrum.[67]

1-(4-(1,3,2-Dioxaborolan-2-yl)phenyl)ethanone



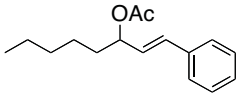
1-(4-(1,3,2-Dioxaborolan-2-yl)phenyl)ethanone was synthesized according to a previously reported procedure and the ^{1}H-NMR spectrum was compared to the previously reported spectrum.[67]

2-*o*-Tolyl-1,3,2-dioxaborolane



2-*o*-Tolyl-1,3,2-dioxaborolane was synthesized according to a previously reported procedure and the ^{1}H-NMR spectrum was compared to the previously reported spectrum.[67]

Procedure for the synthesis of (*E*)-1-phenyloct-1-en-3-yl acetate (**3**) under initial conditions (Figure 2.16)



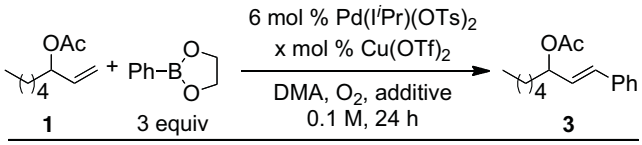
To an oven-dried 50 mL round bottom Schlenk flask equipped with a stir bar was added 25 mg Pd(I^{i}Pr)(OTs)$_2$ (0.030 mmol, 0.06 equiv.), 45 mg Cu(OTf)$_2$ (0.016 mmol, 0.25 equiv.), and 250 mg powdered freshly activated 3 Å MS. The flask was flushed with nitrogen before adding 3.50 mL DMA. A solution of 85 mg oct-1-en-3-yl acetate (**1**) (0.50 mmol) in 0.50 mL DMA was added via syringe. A three-way joint was fitted with a balloon of O_2 and attached to the flask. The apparatus was evacuated and refilled with oxygen three times. The mixture was stirred under O_2 atmosphere for 5 min. To the stirred mixture was added 222 mg 2-phenyl-1,3,2-dioxaborolane (1.50 mmol, 3.00 equiv.) in 0.75 mL DMA via syringe. After 16 h the mixture was filtered through celite,

rinsed with 15 mL Et_2O, and transferred to a separatory funnel. Fifteen mL distilled water were added, and the aqueous layer was extracted three times with 15 mL Et_2O. The combined organic extracts were washed once with 15 mL of a pH = 8 buffer of NH_4Cl/NH_4OH. They were then washed twice with 15 mL distilled water, then 15 mL brine followed by drying over Na_2SO_4. The mixture was filtered and the solvent was removed in vacuo. (*E*)-1-Phenyloct-1-en-3-yl acetate (**3**) was purified by silica gel flash chromatography eluting with 1% acetone in hexanes and was isolated as a clear oil in 23% yield (28 mg). R_f = 0.47 w/ 5% acetone in hexanes. ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.6 Hz, 3 H), 1.31 (m, 6 H), 1.68 (m, 2 H), 2.08 (s, 3 H), 5.40 (ddd, *J* = 7.5, 7.5, 7.4 Hz, 1 H), 6.12 (dd, *J* = 16.0, 7.5 Hz, 1 H), 6.60 (d, *J* = 16.0 Hz, 1 H), 7.40-7.24 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 21.5, 22.7, 25.0, 31.8, 34.7, 75.0, 126.7, 128.0, 128.0, 128.7, 132.6, 136.6, 170.6. IR (neat): 3027, 2956, 2930, 2859, 1737, 1494, 1450, 1371, 1239, 1018, 965, 748, 693, 668 cm^{-1}. HRMS $C_{16}H_{22}O_2$ $(M+Na)^+$ calcd.; 269.1517 obsd.; 269.1515.

Optimization of oxidative Heck reaction (Table 2.1)

The procedure for the preparation of **3** described above was used with the following modifications. The reaction was performed on 0.20 mmol scale with ~10 wt% tetradecane used as an internal standard. After 24 h aliquots (~50 μL) were removed, passed through a small silica pipet with ether, and analyzed for conversion and product formation by gas chromatography. The modifications described in Table 2.1 were applied in order to optimize the reaction.

Table 2.1. Optimization of the oxidative Heck reaction.



1 3 equiv **3**

entry	additive	temperature	x	% conversion[a]	% yield[a]
1	3 Å MS	rt	25	22	19
2	3 Å MS	40°C	25	>99	85
3	-	40°C	25	98	93
4	-	40°C	20	>99	>99
5[b]	-	40°C	20	<1	<1
6	-	40°C	0	64	12
7[c]	-	40°C	20	5	5

[a]Conversion and yield were calculated by comparing starting material and product peak integrations to the integration of an intern standard using GC analysis. [b]No Pd(I^{i}Pr)(OTs)$_2$ was used. [c]The reaction was run under nitrogen.

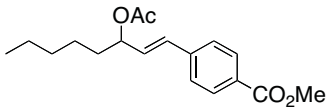
General procedure for the preparation of **3** under optimized conditions

(Table 2.2, entry 1)

To an oven-dried 50 mL round bottom Schlenk flask equipped with a stir bar was added 25 mg Pd(I^{i}Pr)(OTs)$_2$ (0.030 mmol, 0.05 equiv.), and 36 mg Cu(OTf)$_2$ (0.013 mmol, 0.20 equiv). The flask was flushed with nitrogen before adding 3.50 mL DMA. A solution of 85 mg **1** (0.50 mmol) was added in 0.50 mL DMA via syringe. A three-way joint was fitted with a balloon of O_2 and attached to the flask. The apparatus was evacuated and refilled with oxygen three times. The mixture was stirred under O_2 atmosphere for 5 min. To the stirred mixture was added 222 mg 2-phenyl-1,3,2-dioxaborolane (1.50 mmol, 3.00 equiv.) in 0.75 mL DMA via syringe. The mixture was then heated to 40 °C in an oil bath. After 24 h the mixture was diluted with 15 mL Et_2O and transferred to a separatory funnel. Fifteen mL distilled water were added, and the aqueous layer was extracted three times with 15 mL Et_2O. The combined organic

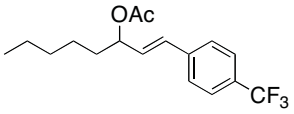
extracts were washed once with a pH = 8 buffer of NH_4Cl/NH_4OH. They were then washed twice with 15 mL distilled water then 15 mL brine followed by drying over Na_2SO_4. The mixture was filtered and the solvent was removed in vacuo. The product was purified by silica gel flash chromatography eluting with 1% acetone in hexanes and was isolated as a clear oil in 92-98% yield (113 mg and 121 mg).

Table 2.2 entry 2 ((*E*)-methyl 4-(3-acetoxyoct-1-en-1-yl) benzoate) (**4**)



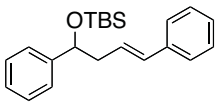
The general procedure for the preparation of **3** was used with the modifications that 309 mg methyl 4-(1,3,2-dioxaborolan-2-yl)benzoate (1.5 mmol, 3.0 equiv) was used, and the mixture was stirred at 45 ºC for 23 h before workup. The product was purified by silica gel flash chromatography eluting with 2% acetone in hexanes to give **4** as a clear oil in 97% yield (147 mg and 148 mg). R_f = 0.24 w/ 5% acetone in hexanes. IR (neat): 2391, 2859, 1719, 1607, 1435, 1413, 1370, 1276, 1234, 1178, 1108, 1016, 958, 869 763, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.6 Hz, 3 H), 1.31 (m, 6 H), 1.69 (m, 2 H), 2.09 (s, 3 H), 3.91 (s, 3 H), 5.41 (ddd, *J* = 7.1, 7.1, 7.0 Hz, 1 H), 6.24 (dd, *J* = 16.0, 7.1 Hz, 1 H), 6.62 (d, *J* = 16.0 Hz, 1 H), 7.43 (d, *J* = 8.1 Hz, 2 H), 7.98 (d, *J* = 8.3 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 21.5, 22.7, 25.0, 31.7, 34.6, 52.2, 74.6, 126.6, 129.4, 130.1, 130.8, 131.3, 141.0, 167.0, 170.5. HRMS $C_{18}H_{24}O_4$ $(M+Na)^+$ calcd.; 327.1572 obsd.; 327.1577.

Table 2.2, entry 3 ((*E*)-1-(4-(trifluoromethyl)phenyl)oct-1-en-3-yl acetate) (**5**)



The general procedure for the preparation of **3** was used with the modifications that 324 mg 2-(4-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (1.5 mmol, 3.0 equiv) was used, and the mixture was stirred at 45 ºC for 22 h before workup. The product was purified by silica gel flash chromatography eluting with 1% acetone in hexanes to give **5** as a clear oil in 70-75% yield (110 mg and 118 mg). R_f = 0.49 w/ 5% acetone in hexanes. IR (neat): 2933, 2861, 1735, 1616, 1457, 1415, 1372, 1322, 1234, 1163, 1121, 1108, 1066, 1015, 967, 952, 897, 860, 815, 634 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, *J* = 7.1 Hz, 3 H), 1.28 (m, 6 H), 1.66 (m, 2 H), 2.06 (s, 3 H), 5.38 (ddd, *J* = 7.1, 7.1, 6.9 Hz, 1 H), 6.19 (dd, *J* = 15.9, 7.1 Hz, 1 H), 6.59 (d, *J* = 16.0 Hz, 1 H), 7.44 (br d, *J* = 8.1 Hz, 2 H), 7.53 (br d, *J* = 8.2 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 21.5, 22.7, 25.0, 31.7, 34.6, 74.6, 124.3 (q, *J* = 271.4 Hz), 125.7 (q, *J* = 3.5 Hz), 126.9, 129.8 (q, *J* = 32.2 Hz), 130.9 (d, *J* = 9.1 Hz), 140.1, 170.6. HRMS $C_{17}H_{21}F_3O_2$ $(M+Ag)^+$ calcd.; 421.0545 obsd.; 421.0554.

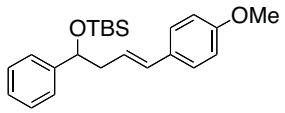
Table 2.2, entry 4 ((*E*)-*tert*-butyl((1,4-diphenylbut-3-en-1-yl)oxy)dimethylsilane) (**6**)



The general procedure for the preparation of **3** was used with the modifications that 131 mg *tert*-butyldimethyl((1-phenylbut-3-en-1-yl)oxy)silane (0.50 mmol) and 222 mg 2-phenyl-1,3,2-dioxaborolane (1.5 mmol, 3.0 equiv) were used, and the mixture was stirred at 35 ºC for 24 h before workup. The product was purified by silica gel flash

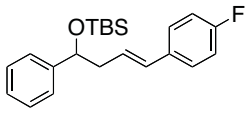
chromatography eluting with 1% acetone in hexanes to give **6** as a clear oil in 76-85% yield (129 mg and 144 mg). The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[10]

Table 2.2, entry 5 ((*E*)-*tert*-butyl((4-(4-methoxyphenyl)-1-phenylbut-3-en-yl)oxy)dimethylsilane) (**7**)



The general procedure for the preparation of **3** was used with the modifications that 131 mg *tert*-butyldimethyl((1-phenylbut-3-en-1-yl)oxy)silane (0.50 mmol) and 267 mg 2-(4-methoxyphenyl)-1,3,2-dioxaborolane (1.5 mmol, 3.0 equiv) were used, and the mixture was stirred at 35 ºC for 24 h before workup. The product was purified by silica gel flash chromatography eluting with 2% acetone in hexanes to give **7** as a clear oil in 78-81% yield (144 mg and 149 mg). The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[10]

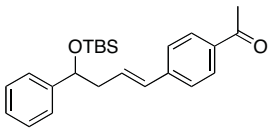
Table 2.2, entry 6 ((*E*)-*tert*-butyl((4-(4-fluorophenyl)-1-phenylbuty-3-en-1-yl)oxy)dimethylsilane) (**8**)



The general procedure for the preparation of **3** was used with the modifications that 131 mg *tert*-butyldimethyl((1-phenylbut-3-en-1-yl)oxy)silane (0.50 mmol) and 249 mg 2-(4-fluorophenyl)-1,3,2-dioxaborolane (1.5 mmol, 3.0 equiv) were used, and the

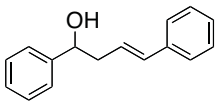
mixture was stirred at 45 ºC for 24 h before workup. The product was purified by silica gel flash chromatography eluting with 1% acetone in hexanes to give **8** as a clear oil in 87% yield (156 mg and 155 mg). The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[10]

Table 2.2, entry 7 ((*E*)-1-(4-(4-((*tert*-butyldimethylsilyl)oxy)-4-phenylbut-1-en-1-yl)phenyl)ethanone) (**9**)



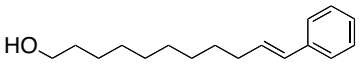
The general procedure for the preparation of **3** was used with the modifications that 131 mg *tert*-butyldimethyl((1-phenylbut-3-en-1-yl)oxy)silane (0.50 mmol) and 285 mg 1-(4-(1,3,2-dioxaborolan-2-yl)phenyl)ethanone (1.5 mmol, 3.0 equiv) were used, and the mixture was stirred at 45 ºC for 23 h before workup. The product was purified by silica gel flash chromatography eluting with 2% acetone in hexanes to give **9** as a clear oil in 77-78% yield (146 mg and 149 mg). R_f = 0.38 w/5% acetone in hexanes. IR (neat): 3031, 2954, 2928, 2894, 2856, 1682, 1602, 1493, 1471, 1409, 1358, 1267, 1181, 1091, 1068, 1005, 967, 955, 938, 836, 776, 700, 668, 592, 545 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ -0.13 (s, 3 H), 0.01 (s, 3 H), 0.88 (s, 9 H), 2.67-1.50 (m, 5 H), 4.76 (dd, *J* = 7.4, 5.0 Hz, 1 H), 6.45-6.30 (m, 2 H), 7.27-7.24 (m, 1 H), 7.33 (br d, *J* = 4.4 Hz, 4 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 7.89 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.7, -4.5, 18.4, 26.0, 26.7, 45.0, 75.1, 125.9, 126.1, 127.3, 128.3, 128.9, 130.7, 131.5, 135.7, 142.5, 145.1, 197.7. HRMS $C_{24}H_{32}O_2Si$ $(M+Na)^+$ calcd.; 403.2069 obsd.; 403.2078.

Table 2.2, entry 8 ((*E*)-1,4-diphenylbut-3-en-1-ol (**10**)



The general procedure for the preparation of **3** was used with the modifications that 74 mg 1-phenylbut-3-en-1-ol (0.50 mmol) and 222 mg 2-phenyl-1,3,2-dioxaborolane (1.5 mmol, 3.0 equiv) were used, and the mixture was stirred at 40 ºC for 20 h before workup. The product was purified by silica gel flash chromatography eluting with 10% acetone in hexanes to give **10** as a white solid (mp = 84-86 ºC) in 58-67% yield as a mixture of ~10:1 *E*-styrene:all other isomers (65 mg and 75 mg). R_f = 0.45 w/ 20% acetone in hexanes. IR (neat): 3365, 3059, 3027, 2927, 1598, 1494, 1450, 1046, 1027, 966, 913, 742, 699, 538 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.06 (br s, 1 H), 2.70-2.65 (m, 2 H), 4.82 (br t, *J* = 5.9 Hz, 1 H), 6.21 (dt, *J* = 15.7, 7.4 Hz, 1 H), 6.51 (d, *J* = 16.0 Hz, 1 H), 7.42-7.20 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.3, 73.9, 126.0, 126.1, 126.4, 127.5, 127.8, 128.7, 128.7, 133.6, 137.4, 144.1. HRMS $C_{16}H_{16}O$ $(M+Na)^+$ calcd.; 247.1099 obsd.; 247.1105.

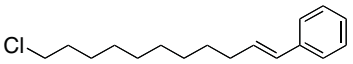
Table 2.2, entry 9 ((*E*)-11-phenylundec-10-en-1-ol) (**11**)



The general procedure for the preparation of **3** was used with the modifications that 85 mg undec-10-en-1-ol (0.50 mmol) and 222 mg 2-phenyl-1,3,2-dioxaborolane (1.5 mmol, 3.0 equiv) were used, and the mixture was stirred at 35 ºC for 22 h before workup. The product was purified by silica gel flash chromatography eluting with 5% acetone in hexanes to give **11** as a white solid (mp = 32-33 ºC) in 78-81% yield as a mixture of ~10:1 *E*-styrene:all other isomers (96 mg and 100 mg). R_f = 0.11 w/ 5% acetone in

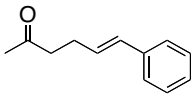
hexanes. IR (neat): 3315, 3024, 2924, 2853, 1494, 1456, 1056, 964, 742, 692, 668 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.57-1.26 (m, 15 H), 2.21 (m, 2 H), 3.64 (t, *J* = 6.5 Hz, 2 H), 6.22 (dt, *J* = 15.8, 6.6 Hz, 1 H), 6.38 (d, *J* = 16.0 Hz, 1 H), 7.39-7.16 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9, 29.4, 29.6, 29.6, 29.6, 29.7, 33.0, 33.2, 63.3, 126.1, 126.9, 128.7, 129.9, 131.4, 138.1. HRMS $C_{17}H_{26}O$ $(M+Na)^+$ calcd.; 269.1881 obsd.; 269.1887.

Table 2.2, entry 10 ((*E*)-(11-chloroundec-1-en-1-yl)benzene (**12**)



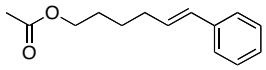
The general procedure for the preparation of **3** was used with the modifications that 94 mg 11-chloroundec-1-ene (0.50 mmol) and 222 mg 2-phenyl-1,3,2-dioxaborolane (1.5 mmol, 3.0 equiv) were used, and the mixture was stirred at 35 ºC for 22 h before workup. The product was purified by silica gel flash chromatography eluting with hexanes to give **12** as a clear oil in 88-89% yield as a mixture of ~10:1 *E*-styrene:all other isomers (116 mg and 118 mg). R_f = 0.64 w/ 1% acetone in hexanes. IR (neat): 3024, 2924, 2852, 1652, 1598, 1494, 1447, 1308, 10711, 1028, 963, 909, 741, 692, 651 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.47-1.26 (m, 12 H), 1.77 (quint, *J* = 6.7 Hz, 2 H), 2.20 (m, 2 H), 3.53 (t, *J* = 6.8 Hz, 2 H), 6.22 (dt, *J* = 15.7, 6.6 Hz, 1 H), 6.38 (d, *J* = 15.7 Hz, 1 H), 7.40-7.16 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.1, 29.1, 29.4, 29.5, 29.6, 32.8, 33.2, 45.4, 126.1, 126.9, 128.7, 129.9, 131.3, 138.1. HRMS $C_{17}H_{25}Cl$ $(M+Ag)^+$ calcd.; 371.0696 obsd.; 371.0709.

Table 2.2, entry 11 ((*E*)-6-phenylhex-5-en-2-one) (**13**)



The general procedure for the preparation of **3** was used with the modifications that 49 mg hex-5-en-2-one (0.50 mmol) and 222 mg 2-phenyl-1,3,2-dioxaborolane (1.5 mmol, 3.0 equiv) were used, and the mixture was stirred at 35 ºC for 21 h before workup. The product was purified by silica gel flash chromatography eluting with 2% acetone in hexanes to give **13** as a clear oil in 68-70% yield (59 mg and 61 mg). R_f = 0.34 w/ 5% acetone in hexanes. IR (neat): 3025, 2916, 1712, 1598, 1576, 1492, 1447, 1363, 1159, 1070, 966, 748, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.18 (s, 3 H), 2.52-2.45 (m, 2 H), 2.64-2.60 (m, 2 H), 6.20 (dt, J = 15.9, 6.7 Hz, 1 H), 6.40 (d, J = 15.8 Hz, 1 H), 7.35-7.17 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.3, 30.2, 43.3, 126.2, 127.3, 128.7, 129.0, 130.9, 137.5, 208.3. HRMS $C_{12}H_{14}O$ $(M+Na)^+$ calcd.; 197.0942 obsd.; 197.0944.

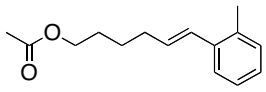
Table 2.2, entry 12 ((*E*)-6-phenylhex-5-en-1-yl acetate) (**14**)



The general procedure for the preparation of **3** was used with the modifications that 71 mg hex-5-en-1-yl acetate (0.50 mmol) and 222 mg 2-phenyl-1,3,2-dioxaborolane (1.5 mmol, 3.0 equiv) were used, and the mixture was stirred at 35 ºC for 22 h before workup. The product was purified by silica gel flash chromatography eluting with 2% acetone in hexanes to give **14** as a clear oil in 86-88% yield as a mixture of ~10:1 *E*-styrene:all other isomers (94 mg and 96 mg). R_f = 0.42 w/ 5% acetone in hexanes. IR (neat): 3025, 2937, 1736, 1494, 1448, 1365, 1235, 1038, 966, 745, 694, 606 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.59-1.49 (m, 2 H), 1.74-1.65 (m, 2 H), 2.06 (s, 3 H), 2.25

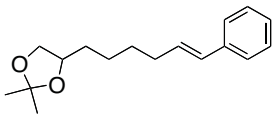
(dt, *J* = 7.2, 7.1 Hz, 2 H), 4.09 (t, *J* = 6.6 Hz, 2 H), 6.21 (dt, *J* = 15.8, 6.8 Hz, 1 H), 6.41 (d, *J* = 15.7 Hz, 1 H), 7.39-7.17 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 25.8, 28.2, 32.7, 64.5, 126.1, 127.1, 128.6, 130.3, 130.5, 137.8, 171.3. HRMS $C_{14}H_{18}O_2$ $(M+Na)^+$ calcd.; 241.1204 obsd.; 241.1208.

Table 2.2, entry 13 ((*E*)-6-(*o*-tolyl)hex-5-en-1-yl acetate) (**15**)



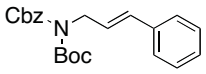
The general procedure for the preparation of **3** was used with the modifications that 71 mg hex-5-en-1-yl acetate (0.50 mmol) and 243 mg 2-(*o*-tolyl)-1,3,2-dioxaborolane (1.5 mmol, 3.0 equiv) were used in the presence of 42 mg $Pd(I^iPr)(OTs)_2$ (0.050 mmol, 0.10 equiv). The mixture was stirred at 75 ºC for 23 h before workup. The product was purified by silica gel flash chromatography eluting with 2% acetone in hexanes to give **15** as a clear oil in 79-83% yield as a mixture of ~10:1 *E*-styrene:all other isomers (92 mg and 97 mg). R_f = 0.38 w/ 5% acetone in hexanes. IR (neat): 3018, 2937, 1737, 1485, 1458, 1365, 1236, 1037, 967, 747, 606 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59-1.51 (m, 2 H), 1.76-1.66 (m, 2 H), 2.06 (s, 3 H), 2.33-2.24 (m, 5 H), 4.10 (t, *J* = 6.5 Hz, 2 H), 6.07 (dt, *J* = 15.6, 7.1 Hz, 1 H), 6.59 (d, *J* = 15.7 Hz, 1 H), 7.24-7.12 (m, 3 H), 7.42-7.39 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.0, 21.2, 25.9, 28.3, 33.0, 64.6, 125.6, 126.2, 127.1, 128.4, 130.4, 131.8, 135.1, 137.0, 171.4. HRMS $C_{15}H_{20}O_2$ $(M+Na)^+$ calcd.; 255.1361 obsd.; 255.1366.

Table 2.2, entry 14 ((*E*)-2,2-dimethyl-4-(6-phenylhex-5-en-1-yl)-1,3-dioxolane) (**16**)



The general procedure for the preparation of **3** was used with the modifications that 92 mg 4-(hex-5-en-1-y)-2,2-dimethyl-1,3-dioxolane (0.50 mmol) and 222 mg 2-phenyl-1,3,2-dioxaborolane (1.5 mmol, 3.0 equiv) were used and the mixture was stirred at 35 ºC for 22 h before workup. The product was purified by silica gel flash chromatography eluting with 2% acetone in hexanes to give **16** as a clear oil in 88-90% yield as a mixture of ~10:1 *E*-styrene:all other isomers (114 mg and 117 mg). R_f = 0.53 w/ 5% acetone in hexanes. IR (neat): 3024, 2984, 2931, 2858, 1598, 1494, 1452, 1378, 1368, 1244, 1213, 1154, 1055, 964, 855, 745, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.72-1.19 (m, 12 H), 2.22 (dt, *J* = 6.9, 6.8 Hz, 2 H), 3.51 (t, *J* = 7.0 Hz, 1 H), 4.13-4.02 (m, 2 H), 6.21 (dt, *J* = 15.8, 6.7 Hz, 1 H), 6.38 (d, *J* = 15.9 Hz, 1 H), 7.47-7.16 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5, 25.9, 27.1, 29.5, 33.0, 33.6, 69.6, 76.1, 108.7, 126.0, 126.9, 128.6, 130.1, 130.7, 137.9. HRMS $C_{17}H_{24}O_2$ $(M+Na)^+$ calcd.; 283.1674 obsd.; 283.1692.

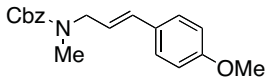
Table 2.2, entry 15 ((*E*)-*N*-Cbz-*N*-Boc-3-phenylprop-2-en-1-amine) (**17**)



The general procedure for the preparation of **3** was used with the modifications that 146 mg *N*-Cbz-*N*-Boc-prop-2-en-1-amine (0.50 mmol) and 222 mg 2-phenyl-1,3,2-dioxaborolane (1.5 mmol, 3.0 equiv) were used and the mixture was stirred at 40 ºC for 21 h before workup. The product was purified by silica gel flash chromatography eluting with 2% acetone in hexanes to give **17** as a white solid (mp = 42-44 ºC) in 88-90% yield

yield (162 mg and 166 mg). R_f = 0.38 w/ 10% acetone in hexanes. IR (neat): 3029, 2978, 1791, 1748, 1719, 1695, 1477, 1368, 1350 1332, 1300, 1216 1152, 1107, 967, 778, 695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.49 (s, 9 H), 4.40 (br d, *J* = 6.3 Hz, 2 H), 5.24 (s, 2H), 6.20 (dt, *J* = 16.0, 6.4 Hz, 1 H), 6.50 (d, *J* = 15.9 Hz, 1 H), 7.42-7.22 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.2, 48.4, 68.6, 83.2, 124.7, 125.0, 126.6, 127.8, 128.4, 128.5, 128.7, 132.9, 135.7, 136.7, 152.0, 153.8. HRMS $C_{22}H_{25}NO_4$ $(M+Na)^+$ calcd.; 390.1681 obsd.; 390.1686.

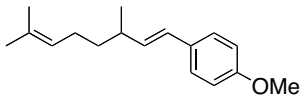
Table 2.2, entry 16 ((*E*)-benzyl (3-(4-methoxyphenyl)allyl)methylcarbamate) (**18**)



The general procedure for the preparation of **3** was used with the modifications that 103 mg benzyl allyl(methyl)carbamate (0.50 mmol) and 267 mg 2-(4-methoxyphenyl)-1,3,2-dioxaborolane (1.5 mmol, 3.0 equiv) were used, and the mixture was stirred at 40 ºC for 24 h before workup. The product was purified by silica gel flash chromatography eluting with 5% acetone in hexanes to give **18** as a clear oil in 44-46% yield as a mixture of rotomers. (69 mg and 72 mg). 43-45% Starting material was recovered using column chromatography (44 mg and 46 mg). R_f = 0.28 w/ 10% acetone in hexanes. IR (neat): 3022, 2934, 2836, 1699, 1653, 1608, 1558, 1511, 1420, 1401, 1363, 1288, 1247, 1142, 1033, 968, 839, 767, 698 cm^{-1}. ^1H NMR (400 MHz, DMSO-D_6, 55 ºC): δ 2.88 (br s, 3 H), 3.76 (s, 3 H), 3.99 (dd, *J* = 6.2, 1.1 Hz, 2 H), 5.10 (s, 2 H), 6.07 (dt, *J* = 15.8, 6.1 Hz, 1 H), 6.44 (d, *J* = 16.0 Hz, 1 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 7.37-7.29 (m, 7 H). ^{13}C NMR (100 MHz, DMSO-D_6, 55 ºC): δ 162.2, 162.2, 158.8, 155.2, 136.9,

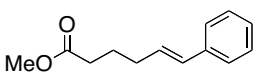
131.1, 128.9, 128.1, 127.4, 127.3, 122.4, 122.3, 113.9, 113.8, 66.0, 55.0, 54.9, 50.1. HRMS $C_{19}H_{21}NO_3$ $(M+Na)^+$ calcd.; 334.1419 obsd.; 334.1424.

Table 2.2, entry 17 ((*E*)-1-(3,7-dimethylocta-1,6-dien-1-yl)-4-methoxybenzene) (**19**)



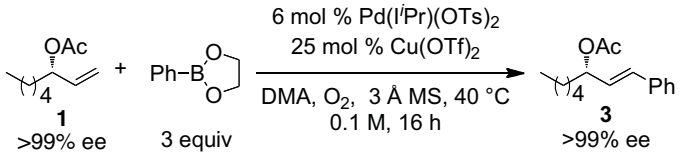
The general procedure for the preparation of **3** was used with the modifications that 69 mg citronellene (0.50 mmol) and 267 mg 2-(4-methoxyphenyl)-1,3,2-dioxaborolane (1.5 mmol, 3.0 equiv) were used, and the mixture was stirred at 55 ºC for 24 h before workup. The product was purified by silica gel flash chromatography eluting with 1% acetone in hexanes to give **19** as a clear oil in 29-33% yield as a mixture of ~6:1 *E*-styrene:all other isomers (35 mg and 40 mg). The remainder of the mass balance is mainly recovered starting material. R_f = 0.51 w/ 1% acetone in hexanes. IR (neat): 2960, 2912, 1653, 1608, 1511, 1456, 1375, 1300, 1246, 1175, 1107, 1038, 966, 816, 668 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (d, *J* = 6.8 Hz, 3 H), 1.39 (ddd, *J* = 7.9, 7.9, 6.9 Hz, 2 H), 1.59 (br s, 3 H), 1.69 (br s, 3 H) 1.99 (ddd, *J* = 7.9, 7.9, 7.6 Hz, 2 H), 2.31-2.22 (m, 1 H), 3.80 (s, 3 H), 5.14-5.08 (m, 1 H), 5.94 (dd, *J* = 15.8, 7.9 Hz, 1 H), 6.28 (d, *J* = 15.7 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 7.28 (d, *J* = 8.6 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.0, 21.0, 26.0, 26.1, 37.0, 37.5, 55.5, 114.1, 124.9, 127.2, 127.7, 131.0, 131.6, 134.9, 158.8. HRMS $C_{17}H_{24}O$ $(M+Ag)^+$ calcd.; 351.0878 obsd.; 351.0889.

Table 2.2, entry 18 ((*E*)-methyl 6-phenylhex-5enoate) (**20**)



The general procedure for the preparation of **3** was used with the modifications that 64 mg methyl 5-hexenoate (**21**) (0.50 mmol) and 222 mg 2-phenyl-1,3,2-dioxaborolane (1.5 mmol, 3.0 equiv) were used, and the mixture was stirred at 40 ºC for 22 h before workup. The product was purified by silica gel flash chromatography eluting with 1% acetone in hexanes to give **20** as a clear oil in 92-98% yield as a mixture of 10:1 *E*-styrene:all other isomers (100 mg and 94 mg). The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[51]

Evaluation of retention of enantiomeric excess



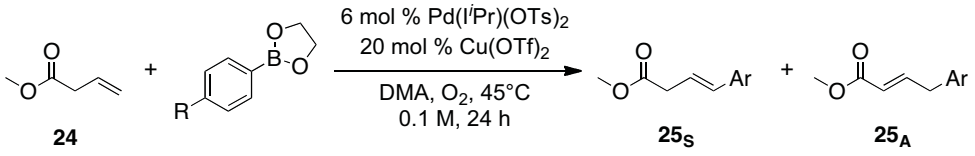
The same procedure used to synthesize racemic **3** was used except 43 mg (*S*)-oct-1-en-3-yl acetate (0.25 mmol) was added, and the product was purified after 18 h by silica gel chromatography by eluting with 1% acetone in hexanes. The purified product was evaluated for enantiomeric excess using chiral SFC (see below).

compound	method	retention times (min)
1	GC hold 100 °C 25 min	2.8 and 2.9
3	SFC 1% MeOH 2 mL/min	4.7 and 5.6

Comparison of selectivities of Pd(II) catalysts commonly used for oxidative Heck reactions

The general procedure for the preparation of **3** was used with the following modifications. The reaction was performed on 0.2 mmol scale (using 200 μL of a 1.0 M standard solution of methyl-5-hexenoate (**21**) w/10 wt% tetradecane as internal standard) and 400 μL of a 1.5 M standard solution of 2-phenyl-1,3,2-dioxaborolane (0.6 mmol, 3 equiv) were used. The mixture was stirred at 40 ºC for 22 h before aliquots (~50 μL) were removed, passed through a small silica pipet with ether, and analyzed for conversion, product formation, and selectivity by gas chromatography. Further modifications and results are described in Table 2.3.

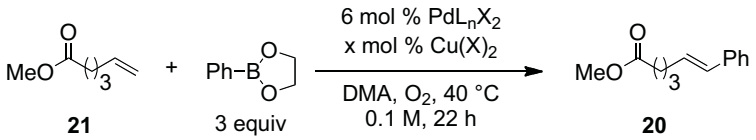
Construction of Hammett plot (Figure 2.19)



24 **25$_S$** **25$_A$**

The general procedure for the preparation of **3** was used with the modifications that 20 mg methyl but-3-enoate **24** (0.2 mmol) and various arylboronic esters (0.6 mmol, 3.0 equiv) were used, and the mixtures were stirred at 45 ºC for 24 h before workup. The crude mixtures were analyzed by ^{1}H NMR to determine the ratio of **25$_S$**:**25$_A$** by comparing the integration of the vinyl or allylic protons of each product.

Table 2.3. Use of common Pd^{II} salts in the oxidative Heck reaction.



entry	Pd^{II} source	Cu^{II} source	% conversion[a]	% yield[a]	selectivity[b]
1	$Pd(MeCN)_2Cl_2$	$CuCl_2$	15.3	<1	-
2	$Pd(OAc)_2$	$Cu(OAc)_2$	>99	35.3	6.2:1
3	$Pd(OAc)_2$	$Cu(OTf)_2$	>99	55.7	2.0:1
4	$Pd(MeCN)_2(OTs)_2$	$Cu(OTf)_2$	>99	99	3.4:1
5	$[Pd(I^iPr)Cl_2]_2$	$Cu(OTf)_2$	79.6	60.8	4.4:1
6	$Pd(I^iPr)(OTs)_2$	$Cu(OTf)_2$	>99	96.3	9.8:1

[a]Conversion and yield were calculated by comparing starting material and product peak integrations to the integration for an internal standard using GC analysis. [b]The selectivity is **20**:all other isomers, as determined by GC analysis.

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CHAPTER 3

DEVELOPMENT AND EVALUATION OF AN (*E*)-STYRENYL-SELECTIVE CLASSICAL HECK REACTION

Introduction

As mentioned in Chapter 2, the classical Heck reaction, which employs Pd^0 as the catalyst, has been more extensively studied and more frequently utilized in target-directed synthesis. In fact, the sheer number of different variants, mechanistic studies, and examples of application to synthesis make the method essentially impossible to comprehensively discuss. However, despite the mechanistic differences, the limitations in substrate compatibility are similar to those that afflict the oxidative Heck reaction. Specifically, the alkene substrate must be electronically biased in order to achieve a high degree of selectivity in migratory insertion and subsequent β-hydride elimination. While the seminal report by Heck was the first example of what later became known as the oxidative Heck reaction, subsequent study was mainly focused on reactions utilizing Pd^0 and aryl halides and pseudohalides as arene sources. Shortly after the seminal report, Heck described a cross-coupling reaction between aryl- and styrenyl-halides and electronically biased olefins in the presence of catalytic amounts of palladium (example shown in Figure 3.1 a).[1] The authors propose a mechanism initiated by oxidative addition of Pd^0 into carbon-halogen bonds, followed by migratory insertion, β-hydride

elimination, and reductive elimination of Pd–H (assisted by the addition of an amine base) (Figure 3.1 b). Both aryl-iodides and aryl-bromides were demonstrated as competent in the reaction, and high selectivity is observed using the electronically biased olefins tested (Figure 3.1 c). The reaction required elevated temperatures, but the olefin substrate was used in only slight excess (in contrast to oxidative conditions). The Pd^0 catalyzed Heck variant has been an intense area of focus by countless groups in the study of organometallic reactions and their application to synthesis. There has historically been a disparity in the level of study, and frequency of utilization between the classical Heck and oxidative Heck reactions. This is likely due to the consistent use of only catalytic amounts of palladium, and decreased excess of either substrate or arene source required for high yielding Pd^0-catalyzed reactions. Despite synthetic chemist's heavy reliance upon this transformation, the synthetic versatility of the classical Heck reaction, like the oxidative Heck reaction, would benefit from the extension of compatible substrates to those bearing electronically nonbiased olefins. The rational design of a catalytic system that is capable of carrying out such transformations is the focus of this chapter.

Background

Aryl iodides undergo oxidative addition to Pd^0 most readily of the halides, and at elevated temperatures, do not require additives to enable the efficient cross-coupling with olefins.[1] This is due to the ease with which these reagents undergo oxidative addition, the rate limiting step in many Heck reactions,[2] as compared to aryl bromides and aryl chlorides, which possess a stronger Ar–X bond.[3] Heck and coworkers expended considerable effort attempting to develop conditions where aryl bromides, and especially

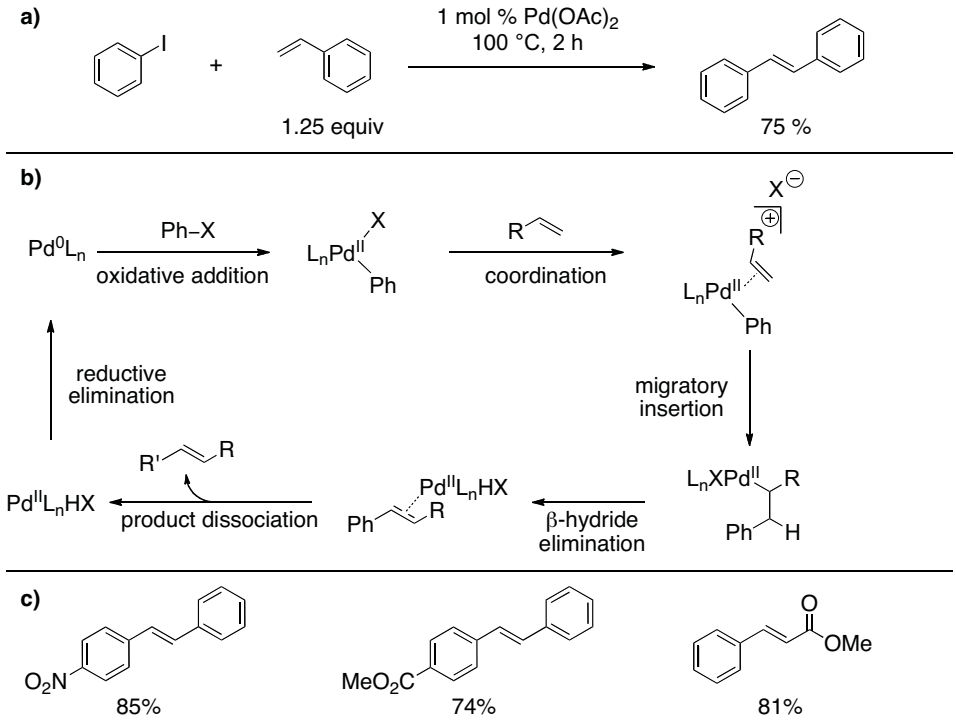


Figure 3.1. a) Classical Heck reaction, **b)** mechanism, and **c)** representative products.

electron rich aryl bromides, performed well in the Heck reaction.[4] A key advancementoccurred upon the discovery that added phosphine ligands allowed previously unreactive arenes to participate in the reaction, presumably due to more facile oxidative addition as a result of the electron donation of the phosphine ligands to palladium. For example, an aryl bromide bearing a highly electron-donating *p*-phenol cross-couples efficiently in the presence of electron rich triarylphosphine ligands (Figure 3.2). The use of these ligands subsequently became commonplace in the performance of classical Heck reactions.[2,3,5-7]

This discovery significantly extended the scope of the Heck reaction, with respect to the aryl halide, and allowed for the development of reactions that require exceptionally low catalyst loadings. Spencer was able to cross couple aryl bromides with electronically biased olefins in moderate to good yield using catalyst loadings of only 0.01 mol % in the

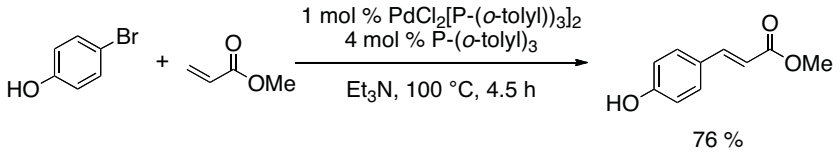


Figure 3.2. Added phosphine ligands allow cross coupling using electron rich aryl bromides.

presence of various phosphine ligands (Figure 3.3).[8] Several other reports have also demonstrated the beneficial use of phosphine ligands when catalysis requires oxidative addition into an Ar–Br bond.[9,10]

Herrmann was able to extend this concept to the use of aryl chlorides, although with limited substrate scope and in moderate yield (Figure 3.4).[11] Improved substrate scope and yields were observed by Fu[12] and Hartwig[13] using the electron-rich P(*t*-Bu)$_3$ ligand in the cross coupling of aryl chlorides with terminal alkenes (Figure 3.5). Finally, various bidentate phosphine ligands have been used successfully to promote oxidative addition into relatively unreactive aryl–halide bonds.[14-18]

Aryl–trifluoromethane sulfonate (ArOTf) bonds also undergo oxidative addition with phosphine-ligated Pd^0, leading to Heck products at elevated temperatures.[19] Some of these products may be difficult to obtain using aryl halides. For example, Hagiwara reported moderate to good yields using a variety of aryl triflates (Figure 3.6), including hindered arenes, those bearing electron donating substituents, and even an aryl chloride.[20] Interestingly, if triethylamine is used as base, the same conditions deliver Michael addition products (i.e., products analogous to those shown in Figure 3.6, except where the olefin is saturated) likely due to a hydride addition with the hydride originating from the amine base.[21,22] More unusual aryl sources include acid chlorides, carboxylic acids, esters, and acid anhydrides.[23-26]

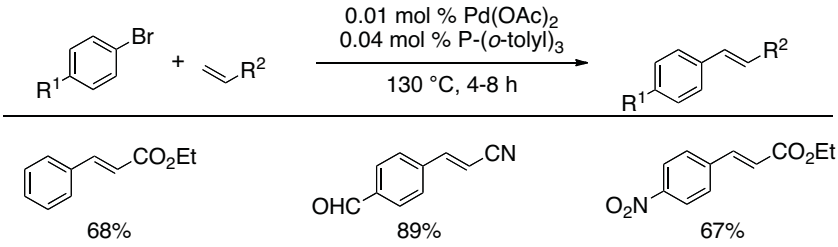


Figure 3.3. Spencer's extension to aryl bromides.

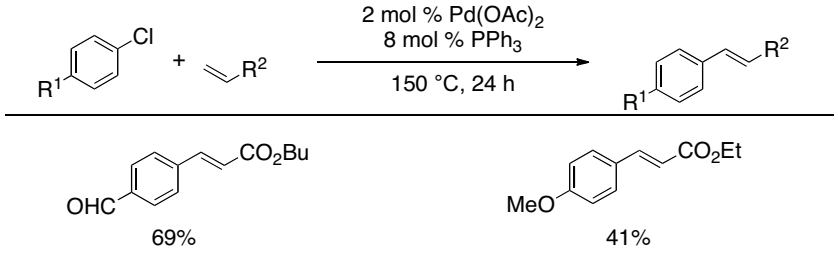


Figure 3.4. Cross coupling with aryl chlorides as demonstrated by Herrmann.

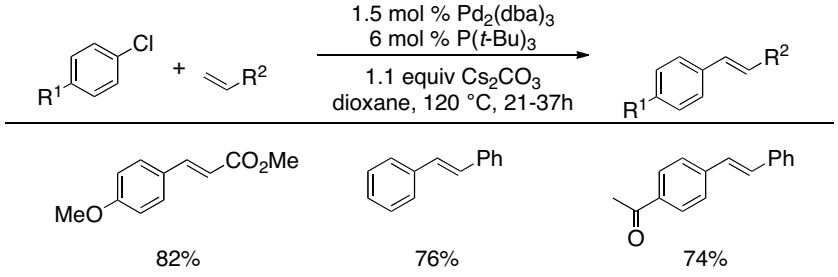


Figure 3.5. Improved results using aryl chlorides when P(*t*-Bu)$_3$ is used as ligand.

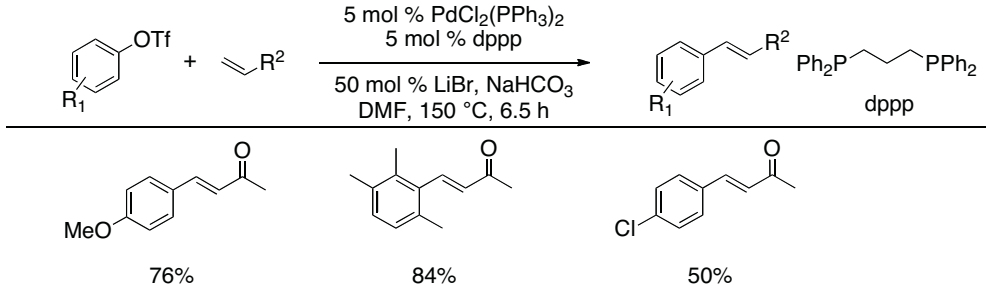


Figure 3.6. Hagiwara's results using aryl triflates.

Jeffrey and coworkers reported that the addition of tetraalkylammonium halide salts could mediate oxidative addition into aryl–halide bonds in the absence of phosphine ligands.[27,28] Interestingly, this reaction may be carried out in aqueous solvent, and the initial proposal for the role of the tetraalkylammonium salts was as phase-transfer catalysts. A subsequent mechanistic study suggested that Pd colloids are formed in the reaction mixture, and are stabilized by the ammonium salts.[29] This protocol, known as Jeffrey's ligandless conditions, has been employed extensively in Heck reactions since the initial discovery. One example, demonstrating the use of these conditions, and also providing a rare instance where a complex mixture is not obtained when electronically non-biased olefins are used, was reported by Larock and coworkers.[30] In this case, alcohol-bearing terminal olefins were submitted Jeffrey's conditions, and saturated aldehyde products were obtained with remarkable selectivity (Figure 3.7). These aldehydes, rather than a mixture of olefin products, are obtained as a result of the Pd–H "walking" down the alkyl chain until an enol is formed, thereafter tautomerizing to the aldehyde products observed. It is thought that β-hydride elimination to form enols is irreversible, which explains why a more complex mixture is not observed.[31]

The Matsuda-Heck reaction

The most reactive aryl sources are aryl diazonium salts, as they undergo oxidative addition at room temperature in the absence of phophine ligands. Matsuda and coworkers pioneered the use of these reagents in Heck reactions, and they noted that the reagents could be prepared in situ from aniline derivatives and *tert*-butyl nitrite.[32,33] Demonstrating the ease with which these reagents undergo oxidative addition, an iodide

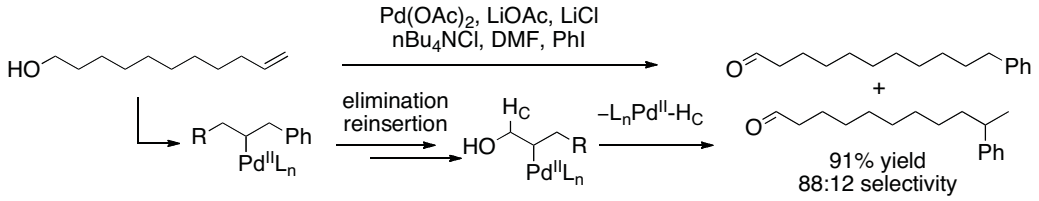


Figure 3.7. Larock's use of Jeffrey conditions, demonstrating a rare case of a selective Heck reaction employing electronically nonbiased olefins.

substituent present on the aryldiazonium salt survives the cross-coupling.[33] Since this report, several other groups have reported success using these reagents,[34-38] and their use has been the subject of reviews,[39,40] and a mechanistic study.[41] Relatively recently, the in-situ formation of the diazonium salts from the corresponding anilines has been the subject of renewed interest.[42] However, as is clear from Figures 3.8 and 3.9, the types of alkene substrates compatible with this method is still limited to polarized olefins. Interestingly, one of the seminal reports by Matsuda regarding the use of aryl diazonium salts in the Heck reaction is also one of the few reports describing results using electronically non-biased olefins.[33] When 1-octene is submitted to his protocol, where the diazonium salt is formed in situ, a 61% yield is observed of a mixture of phenyloctene isomers **1**-**4** (Figure 3.10). This poor selectivity clearly demonstrates the problems associated with existing Heck reactions in terms of substrate compatibility. Finding a solution to this problem could significantly expand the synthetic applications of the Heck reaction.

Intramolecular Heck reactions of nonbiased olefins

As mentioned above, the Pd^0-catalyzed Heck reaction has been much more frequently employed in target directed synthesis than its oxidative counterpart. A likely

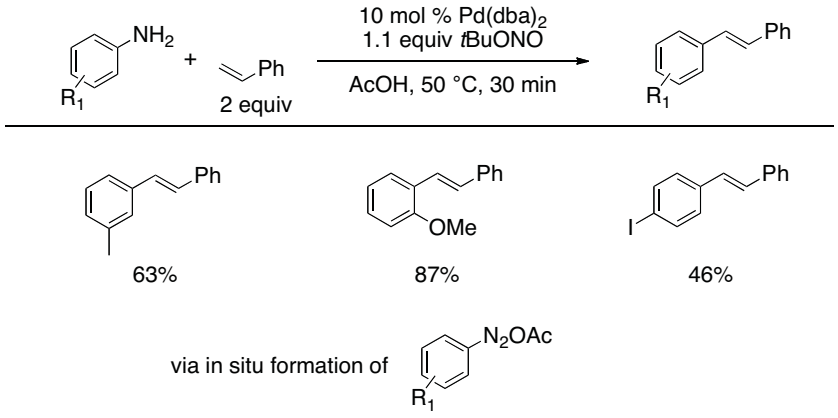


Figure 3.8. Matsuda's use of aryldiazonium salts, formed in situ from anilines.

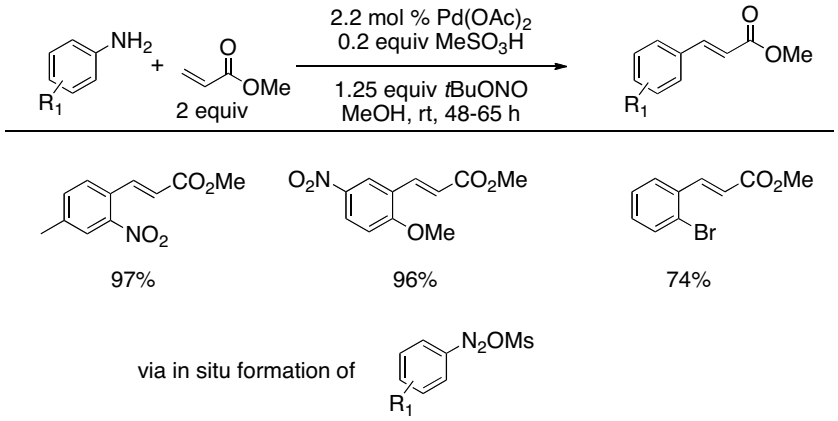


Figure 3.9. Felpin's use of in situ formed diazonium salts, reported in 2011.

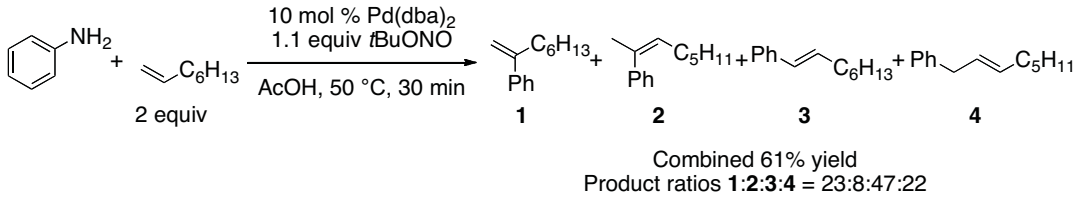


Figure 3.10. Matsuda's results using 1-octene.

reason for this is the fact that the alkene and arene source are typically used in approximately equimolar amounts, instead of either being used in great excess. When coupling two relatively complex segments in a synthesis, it is not appealing to use one in great excess, because this leads to significant waste of precious materials. If the required transformation is an intramolecular Heck reaction, which is frequently the case, excesses of either the aryl source or the olefin are not possible, which eliminates many oxidative Heck variants from consideration. When performing intramolecular Heck reactions, the selectivity of insertion and β-hydride elimination may be influenced more by the ring size of the product and by conformational factors, than by olefin electronics.[43] For example, Overman and coworkers submitted **5** to typical Heck conditions,[44] resulting in delivery of the aryl group to the less electrophillic carbon α to the carbonyl, followed by β-hydride elimination with an exocyclic hydrogen atom yielding **6** (Figure 3.11). The regioselectivity of insertion in this case is controlled by the faster relative rate of formation of a five-membered ring as compared to a 6-membered ring. β-Hydride elimination cannot occur to give a styrene derivative, because there is no hydrogen atom in the benzylic position. Instead, β-hydride elimination results in the exocyclic alkene observed. This intermediate was carried on by Overman and coworkers in the synthesis of asperazine.[44]

Tietze and coworkers successfully employed an electronically nonbiased olefin in an intermolecular Heck reaction, in a total synthesis of estrone (Figure 3.12).[45] In this case the unexpectedly high regioselectivity of migratory insertion is dictated by the conformation of the alkene substrate, **8**. Specifically, the authors propose that high regioselectivity and diastereoselectivity are observed because the arene, **7**, adds to deliver

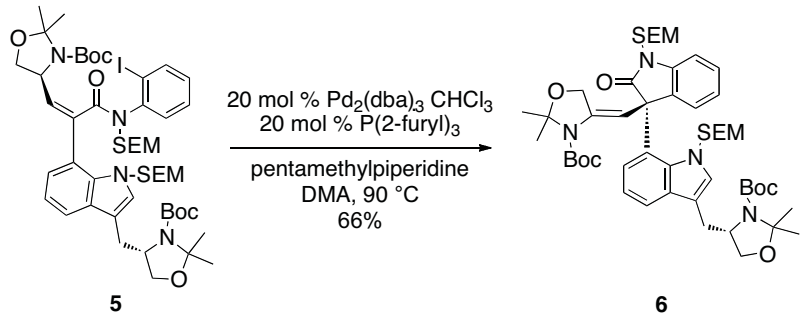


Figure 3.11. Overman's use of an intramolecular Heck reaction with unusual regioselectivity.

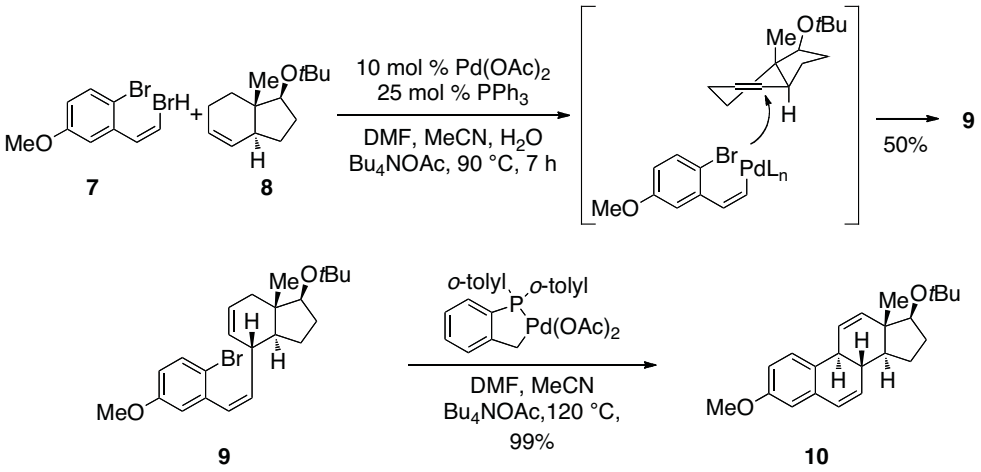


Figure 3.12. Tietze's synthesis of estrone employing both intra-and intermolecular Heck reactions.

a chair-like conformation of the product, and so that the nucleophile avoids the angular methyl group. Following insertion, the catalyst engages the immediately accessible *syn*-hydrogen in β-hydride elimination to deliver **9**. It is important to note that when cyclic alkenes undergo migratory insertion, the newly formed benzylic carbon in intermediate **A** does not bear a hydrogen atom in a *syn* relationship to Pd (Figure 3.13). Therefore, the catalyst does not engage the benzylic hydrogen in β-hydride elimination, and instead eliminates a *syn* hydrogen on the adjacent carbon. In Tietze's synthesis of estrone, the product of the intermolecular Heck reaction is used as a substrate for an intramolecular

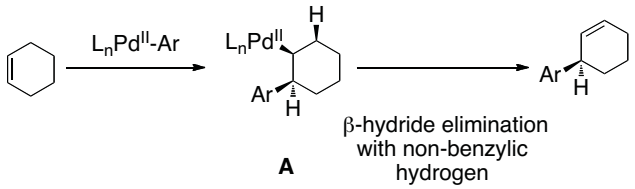


Figure 3.13. Lack of *syn*-hydrogens at the benzylic position of a newly functionalized cyclic alkene substrate.

Heck reaction, where the selectivity is dictated by the ring size of the product, **10** (Figure 3.12).

Chelation-controlled classical Heck reactions

While chelation-controlled classical Heck reactions have not been developed to give such a broadly synthetically useful method as that developed by White and coworkers,[46] there has been some effort in this field. The submission of allylic alcohols to classical Heck conditions typically results in the formation of saturated carbonyl compounds,[47] but this tendency can be overcome under some conditions. For example, Kang and coworkers reported that arylated allylic alcohol products could be obtained by submitting terminal allylic alcohols to classical Heck cross-coupling conditions using hypervalent iodonium salts as the arene source (Figure 3.14).[48] Under these conditions, β-hydride elimination of the carbinol hydrogen is prevented by coordination of the heteroatom to the electrophilic palladium center in intermediate **B**. This coordination prevents a *syn* relationship from occurring between the carbinol hydrogen and the catalyst, and palladium instead engages a benzylic hydrogen atom. This example represents chelation-controlled β-hydride elimination, since the typical ketone product[47] is prevented from forming as a result of substrate coordination to the catalyst.

Hallberg's group reported that the typical regioselectivity of migratory insertion, wherein the arene adds to the terminal carbon of a terminal olefin, may be overridden by chelation of a proximal nitrogen atom (Figure 3.15).[49] In this case, synthetically useful allylic amine products are obtained, due to the catalyst preferring a 5-membered chelate, **C**, with the amine following the bond-forming step. Only one β-hydrogen may be accessed by the catalyst after the substrate-directed migratory insertion event, ultimately resulting in the delivery of 1,1-disubstituted olefin products after product dissociation. While others have reported chelation-controlled Heck reactions,[50-53] these two examples effectively demonstrate how typical insertion and elimination selectivities may be overridden by chelation control.

Hypothesis for the Development of an (*E*)-Styrenyl Selective Classical Heck Reaction and Optimization

Following the successful development of the reaction detailed in Chapter 2, it was anticipated that the insight gained in the mechanistic studies performed on that reaction could be used to develop a Pd^0-catalyzed variant. Briefly, an alkene susceptible to the formation of undesired isomeric products was submitted to a variety of conditions using more traditional Pd^{II} catalysts (Table 2.3). The study indicated that the weakly-coordinating counterions OTf and OTs were essential to obtaining the high selectivity observed. Also, the strongly σ-donating NHC ligand appeared crucial to stabilizing the highly electrophilic catalyst. Based on these observations, it was hypothesized that a similarly selective Pd^0-catalyzed variant could be developed, if an analogous cationic Pd^{II}-alkyl intermediate, **D**, could be delivered following migratory insertion (Figure3.16).

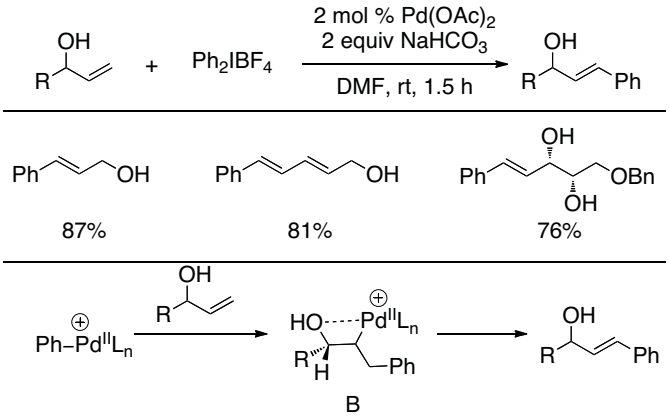


Figure 3.14. Overcoming typical selectivity in β-hydride elimination by employing substrate chelation.

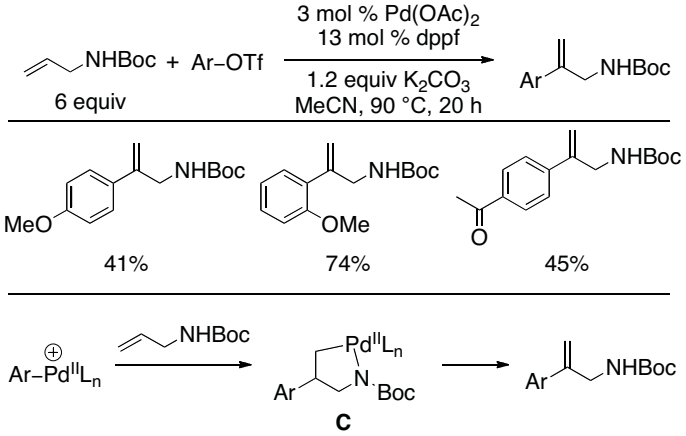


Figure 3.15. Overcoming typical selectivity in migratory insertion by employing chelation control.

Additionally, given the poorer selectivity observed under oxidative conditions at elevated temperatures, it was anticipated that such a selective reaction would have to be performed at mild temperature. It was expected that the solvent used in the oxidative Heck reaction, DMA, would likely be a good choice for the proposed Pd^0-catalyzed variant as well.

These constraints greatly limited the number of reagents and conditions thought to be compatible with a highly selective reaction. Specifically, aryl iodides, bromides and chlorides were eliminated from consideration, due to the halogen's propensity to bind

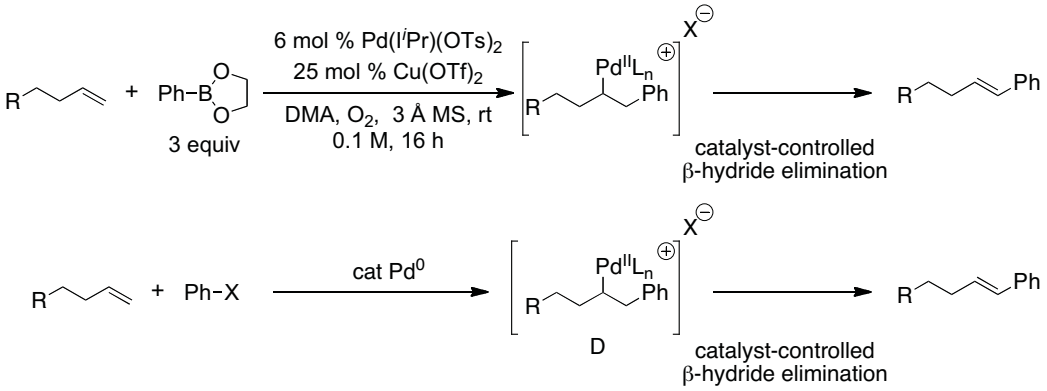
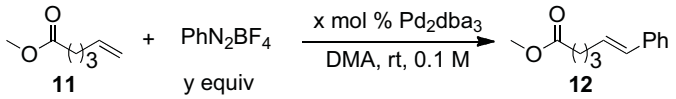


Figure 3.16. Hypothesized Pd-σ-alkyl capable of catalyst-controlled β-hydride elimination, and proposed analogous intermediate arrived at via Pd^0 catalysis.

with palladium.[2] Aryl triflates were considered, because following oxidative addition, the triflate counterion would bind only weakly with palladium. However, these reagents typically require elevated temperatures in order to efficiently engage in oxidative addition, so they also seemed a poor choice. Aryldiazonium salts, however, are well-known to undergo oxidative addition at room temperature, and in the absence of electron rich ligands.[32] In addition, a variety of diazonium salts with different counterions are known, and judicious choice of reagents could result in the required electrophilic Pd^{II}-aryl complex, following oxidative addition.

Aryldiazonium tetrafluoroborates were selected as arene sources, since they are known to be relatively stable, and because the BF_4 counterion coordinates only weakly to palladium. Methyl hex-5-enoate, **11**, was selected as the substrate, because it is susceptible to the formation of undesired product olefin isomers, as discussed in Chapter 2. Initial experiments using this combination of reagents resulted in poor results, giving only modest yield and low selectivity for the desired (*E*)-styrenyl product, **12** (Table 3.1, entry 1). A control experiment (entry 2) excluding the *N*-heterocyclic carbene ligand

Table 3.1. Optimization of Classical Heck Reaction.



11 y equiv **12**

entry	x	y	time	% conversion[a]	% yield[a]	selectivity[b]
1[c]	5	1.5	16 h	>99	68.4	3.8:1
2	5	1.5	16 h	>99	43.3	6.8:1
3	5	1.5	15 min	>99	62.6	7.1:1
4	3	1.5	15 min	>99	86.2	7.5:1
5	3	1.1	15 min	>99	>99	10.7:1
6	0	1.1	15 min	3.6	0	-

[a]Conversion and yield were calculated by comparing starting material and product peak integration to integration of internal standard using corrected GC analysis. Yield refers to the sum of all product isomers [b]Selectivity refers to the ratio of (*E*)-styrene to the sum of all other isomers. [c]12.5 mol % I^{i}Pr carbene added.

delivered higher selectivity, prompting the elimination of this additive in future experiments. A significant disparity between consumption of substrate and product yield dictated the careful monitoring of this ratio over time, revealing reaction completion after only 15 minutes and further consumption (see below for discussion) of the product if the reaction mixture is not quenched (entries 2 vs 3). Finally, decreased catalyst and arene loadings resulted in improved yield and selectivity (entries 4 and 5), while entry 6 confirms that palladium is required.

Scope Evaluation of Classical Heck Reaction

The optimized conditions were evaluated for compatibility with a variety of substrates that perform well under oxidative conditions (see Chapter 2). For example, substrates bearing an ester (Table 3.2, entry 1), a ketone (entry 2) and a silyl ether (entry 3) all proceed with excellent yield and selectivity of products **12**-**14**. A free homoallylic alcohol (entry 4, leading to **15**) is compatible and, more surprisingly, an allylic acetate is an excellent substrate that does not undergo oxidative addition under these conditions

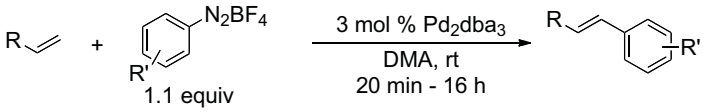
(entry 8, leading to **16**).[54] A doubly-protected allylic amine is a good substrate (entry 6 leading to **17**), however more basic nitrogen functionality, such as a trialkyl amine-containing substrate, was incompatible with these conditions (vide infra). A substrate bearing a distal free alcohol (entry 7) performed well under these conditions, delivering a good yield of **18** after only 40 min. The Pd^{II}-catalyzed conditions are incompatible with carboxylic acids (see Chapter 2), but gratifyingly, **19** and **20** were prepared in good to excellent yield using the present system. Of note, the heteroatom-free substrate dodecene gives excellent results, providing strong evidence that the selectivity observed under these conditions is catalyst-controlled rather than dependent on substrate chelation (entry 10, leading to **21**). A substrate bearing a nitrile (also incompatible with oxidative conditions) is reliably arylated with either a phenyl group or an arene bearing a methyl ester (entries 11 and 12, leading to **22** and **23**). A free 1,2-diol reacts cleanly when installing a phenyl group, but the yield suffers when installing an arene with more steric bulk (cf. entries 13 and 14, leading to **24** and **25**). Free phenols and aryl chlorides are compatible with these conditions (entries 15 and 16, leading to **26** and **27**), and submission of a free allylic alcohol gives the desired product, **28**, but the reaction proceeds more slowly and the yield is diminished due to the formation of a ketone byproduct (vide infra). Interestingly, ketone products such as this are typically the sole product of Heck reactions when allylic alcohols are submitted.[47] Challenging nitro- and iodo-substituted arenes are also compatible under the conditions described, providing valuable handles for further functionalization of products **29** and **30** (entries 18 and 19). The reaction proceeds rapidly and in high yield using α-methylstyrene as the substrate, but unfortunately equimolar mixtures of olefin isomers are observed (entries 20 and 21)

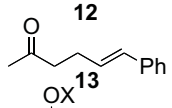
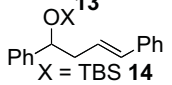
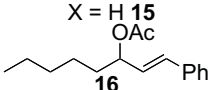
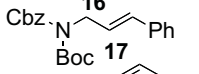
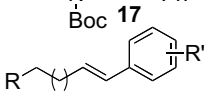
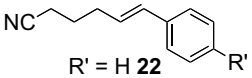
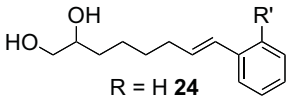
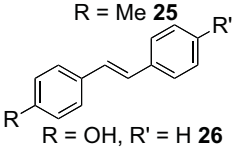
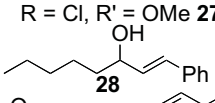
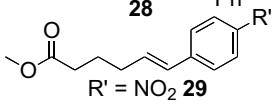
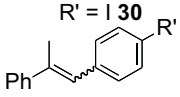
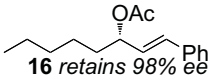
in products **31** and **32**. Finally, a highly enantiomerically enriched substrate, that may be susceptible to racemization, suffers no erosion of enantiomeric excess when submitted to the reaction to prepare **16**.

The free allylic alcohol substrate, **33**, submitted to these conditions, as mentioned above, resulted in a mixture of the desired styrene, **28**, (Table 3.2) along with a ketone byproduct, **34**. This product is shown in Figure 3.17, and is interesting because it suggests that benzylic and carbinol hydrogens undergo competitive β-hydride elimination from **E**. The catalyst engages the carbinol hydrogen in β-hydride elimination, resulting in an enol, **F**, which then tautomerizes to the ketone product observed. This observation was subsequently used to develop a new redox-neutral enantioselective Heck reaction as discussed in Chapter 4. Preliminary evidence suggested that the ratio of styrene to ketone products varied with the electronic nature of the aryldiazonium salt used, but a possible linear free energy relationship was not fully characterized.

While evaluating the scope of this transformation, it was observed that the reaction is highly exothermic raising concerns that the selectivity of a reaction performed on larger scale may suffer. Therefore, on 5 mmol scale, **11** was subjected to the conditions described to prepare **12**, except that the catalyst loading was decreased to 2 mol % and the reaction was performed at -15 ^{o}C (Figure 3.18). Under these conditions, **12** was obtained in comparable yield and improved selectivity for the *E*-styrenyl product after 5.5 h.

Table 3.2. Scope of the Heck reaction.



entry	product	time	% yield[a]
1	**12**	20 min	97[b]
2	 **13**	20 min	89
3	 X = TBS **14**	16 h	87
4	X = H **15**	1.5 h	72
5	 **16**	16 h	87[c]
6	 **17**	16 h	96
7	 R = CH_2OH, R' = H **18**	40 min	77[b]
8	R = CO_2H, R' = H **19**	2 h	95[b]
9	R = CO_2H, R' = 3,5-dimethoxy **20**	2 h	69[b]
10	R = CH_2CH_3, R = H **21**	20 min	77[b]
11	 R' = H **22**	3 h	96
12	R = CO_2Me **23**	3 h	98
13	 R = H **24**	2 h	83
14	R = Me **25**	2 h	66[c]
15	 R = OH, R' = H **26**	1.5 h	98
16	R = Cl, R' = OMe **27**	1.5 h	98
17	 **28**	16 h	55[c,d]
18	 R' = NO_2 **29**	20 min	97
19	R' = I **30**	20 min	66
20	 R' = F **31**	2 h	99[c,e]
21	R' = OMe **32**	2 h	99[c,e]
22	 **16** *retains 98% ee*	16 h	91

[a]Yields are averages of two experiments performed on a 0.5 mmol scale. The selectivity for (*E*)-styrene >20:1 unless otherwise noted. [b]Selectivity for (*E*)-styrene was 10:1. [c]Using 5 mol % Pd_2dba_3 and 1.5 equiv ArN_2BF_4. [d]Isolated 44% ketone product. [e]Obtained ~1:1 mixture of olefin isomers.

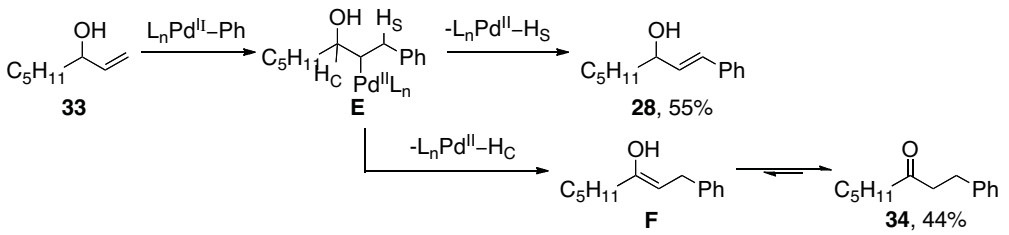


Figure 3.17. Ketone byproduct of the reaction shown in Table 3.2, entry 17, and mechanism of formation.

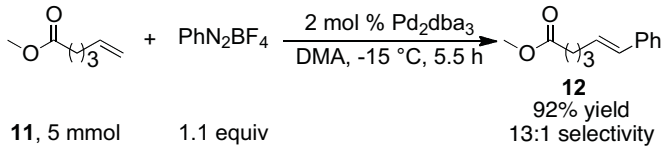


Figure 3.18. Classical Heck reaction scaled up to 5 mmol.

Unsuccessful Pd^0-catalyzed Heck reactions

Several functional groups were found to be incompatible with the formation of diazonium salts, their presence resulting in the rapid decomposition of the reagents. These include anilines bearing an *ortho*-phenol (Figure 3.19), a *para*-acetamide, and 2,6-dialkyl groups. Several olefin substrates were also found to be incompatible with this chemistry. For example, isopulegol, **35**, proved to be a poor substrate, the submission of which resulted in a complex mixture of products (Figure 3.20). Indoles bearing vinyl-substituents, both with a free and a Boc protected nitrogen atom were incompatible, resulting in no consumption of substrate. Submission of *p*-vinyl aniline, and *N,N*-dimethyl allylamine also resulted in the formation of no desired product. Highly substituted and functionalized substrates, **36** and **37**, with 1,1-disubstituted olefins were incompatible, giving no desired product. Finally, those aryldiazonium salts bearing

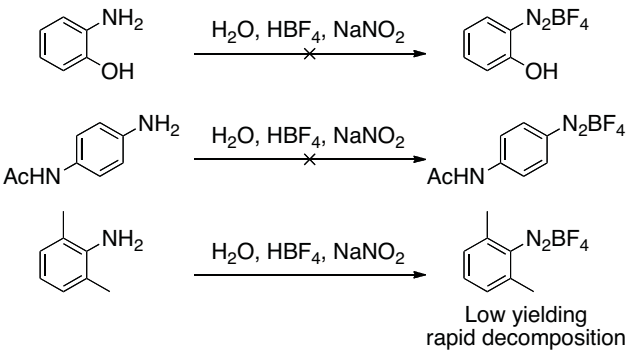


Figure 3.19. Anilines from which diazoniums could not be formed.

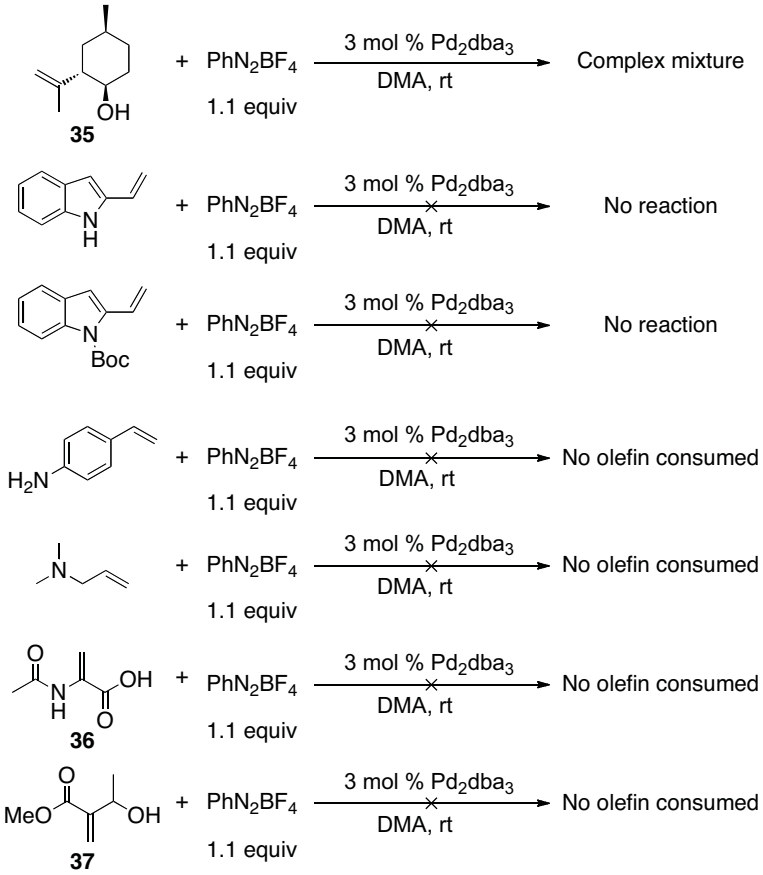


Figure 3.20. Olefin substrates found to be incompatible with Heck reactions.

Lewis basic groups failed to give any desired product when submitted to the conditions developed (Figure 3.21). This included a quinoline derivative, and an arene bearing a sulfonamide group.

Mechanistic Analysis

Given the simplicity of the reaction conditions and the high selectivity observed, a better understanding of what factors are important in achieving high selectivity using traditionally challenging substrates was sought. In this pursuit **11**, an electronically non-biased olefin, was submitted to commonly reported Pd^0-catalyzed Heck conditions (Table 3.3). To directly probe the effect of the counterion, two other common arene sources capable of oxidative addition were evaluated (entries 2 and 3). Unfortunately, the conversion and yields were so low that the data concerning the selectivity is essentially meaningless. Increasing the temperature significantly in order to improve conversion would result in an indirect comparison of conditions, so the effect of counterions has not been meaningfully probed. Interestingly, the effect of solvent on selectivity, which can be examined, is quite dramatic. Acetonitrile or alcoholic solvents are commonly employed in Heck reactions using aryl diazonium salts, but the use of these solvents results in poor yield and selectivity when a non-biased olefin is the substrate (entries 4 and 5).

Having established that the active catalyst described in this report indeed exhibits a unique preference for (*E*)-styrenyl products, a deeper understanding of how the catalyst imparts selectivity was sought. The mechanistic origin of selectivity under oxidative

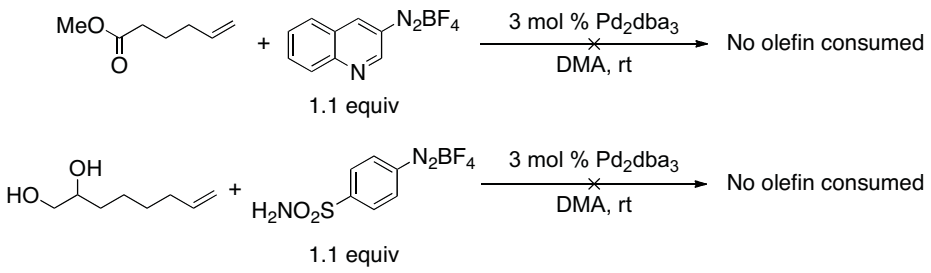
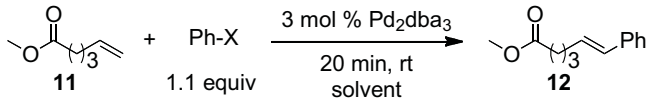


Figure 3.21. Incompetent, but synthetically accessible aryldiazonium salts.

conditions was previously determined by submitting the β,γ-unsaturated ester **38** to Pd^{II}-catalyzed conditions using a variety of electronically disparate arene sources (see Chapter 2); an experiment designed to probe the selectivity-determining β-hydride elimination step where a significant substituent effect was observed. Interestingly, the product distribution measured under Pd^0-catalyzed conditions reveals no clear trend, with styrene products, $\mathbf{39_S}$, favored in similar ratios regardless of the electronic nature of the arene (Figure 3.22). Also intriquing is the fact that allylic products, $\mathbf{39_A}$, were typically favored under oxidative Heck conditions, while they were the minor products under Pd^0-catalyzed conditions, regardless of the arene used.

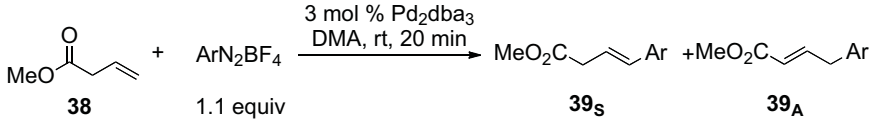
As a direct comparison of the results using oxidative vs Pd^0-catalyzed conditions, the Hammett plot from Chapter 2 is shown (Figure 3.23 a), along with the results under classical conditions. Clearly, this suggests that β-hydride elimination in these two reactions is selective based on different properties of the C–H bond undergoing elimination. To gain a better understanding of the Pd^0-catalyzed reaction, a more sensitive mechanistic experiment was designed, whereby allyl benzene, **40**, was submitted to the optimal conditions with a variety of electronically disparate aryl diazonium salts. In this product-partitioning experiment, the catalyst must distinguish

Table 3.3. Comparison of results observed under more frequently used conditions in classical Heck reactions.



entry	x	solvent	% conversion[a]	% yield[a]	selectivity[b]
1	N_2BF_4	DMA	>99	>99	10.7:1
2[c]	I	DMA	2.5	1.0	1.6:1
3[c]	OTs	DMA	<1	0.1	1.2:1
4	N_2BF_4	MeOH	>99	20	0.2:1
5	N_2BF_4	MeCN	98.1	15	0.3:1

[a]Conversion and yield calculated by comparing starting material and product peak integration to integration of internal standard using GC analysis. [b]Selectivity is (*E*)-styrene:all other isomers. [c]Reaction allowed to stir for 1 h.



Ar	$39_S/39_A$	Ar	$39_S/39_A$
4-H	6.03	4-CO_2Me	7.69
4-NO_2	6.11	4-Br	6.47
4-OMe	7.87	4-F	6.12

Figure 3.22. Attempted product partitioning experiment using substrate **38** under Pd^0-catalyzed conditions.

between two benzylic hydrogens in intermediate **G**, which presumably differ only by virtue of the arenes immediately adjacent (Figure 3.23 b). The linear free energy relationship observed suggests that the origin of selectivity under these conditions is related to the ability of the metal center in intermediate **G** to distinguish between β-hydrogens as a function of their relative *hydridic* nature. Therefore, submission of electron-rich diazonium salts results in relatively more $\mathbf{41_{Ar}}$, due to the greater ability of the newly installed arene to stabilize partial positive charge developing during β-hydride elimination. Consistent with this proposal, submission of electron-deficient aryl diazonium salts results in relatively more $\mathbf{41_{Ph}}$, due to destabilization of partial positive charge by the newly-installed arene. These results contrast markedly with those observed

under oxidative Pd^{II} catalysis, suggesting an interesting mechanistic complementarity along with the more intuitive counterpart arising from the differing oxidation states of the two precatalysts. It should be noted that the product isomers arising from arylation of allyl benzene, **41**, are difficult to distinguish from one another. For this reason, authentic samples of $\mathbf{41_{Ar}}$ products were synthesized using Wittig chemistry (Figure 3.24), so as to conclusively identify these isomers.

Conclusions

In conclusion, simple and efficient conditions have been discovered for a Pd^0-catalyzed Heck reaction that delivers high selectivity for *(E)*-styrenyl products in the absence of substrate bias. This reaction is compatible with a greater range of functional groups than the related Pd^{II} system and utilizes a commercially-available catalyst. Additionally, the reaction requires no base, elevated temperatures, nor additional oxidant. For most substrates evaluated, the reaction is completed rapidly, but the rate is retarded when using substrates with allylic coordinating groups. Some functional groups are incompatible, but it is reasonably easy to predict these, providing another advantage over other Heck protocols, which can require optimization for each substrate. Initial mechanistic experiments suggest that high selectivity is dependent upon the identity of the solvent. A linear free energy relationship probing product distribution as a function of the electronic nature of the introduced arene suggests that this catalyst selects between β-hydrogens based on their hydridic nature, which is in contrast with the Pd^{II} system previously reported. Future computational studies may help to elucidate why cationic palladium is capable of distinguishing between electronically inequivalent β-hydrogens

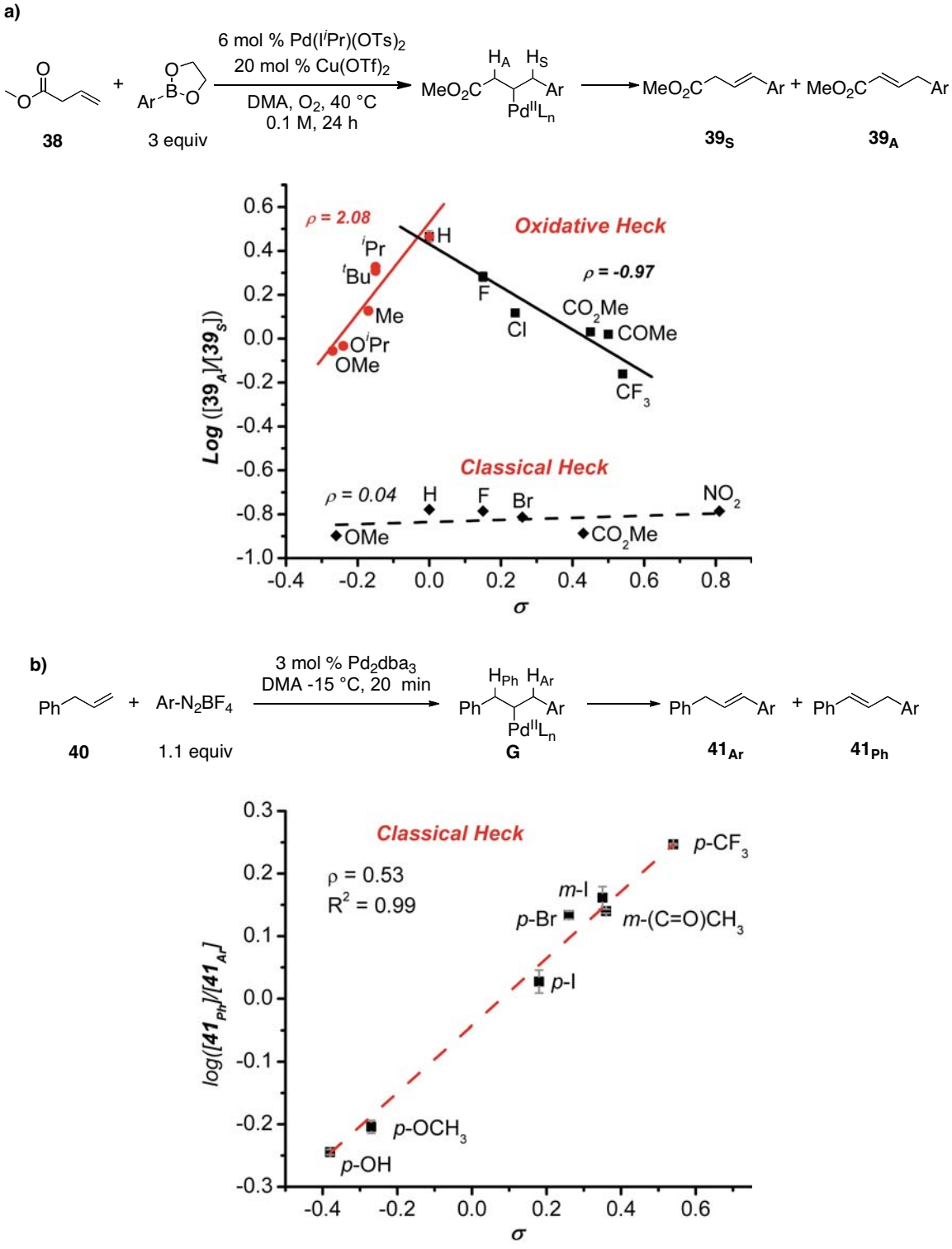


Figure 3.23. a) Comparison of Hammett plots using substrate **38** under oxidative, and classical conditions. **b)** Hammett plot under classical conditions using **40** as substrate.

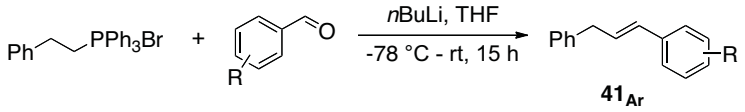


Figure 3.24. Wittig reactions used to prepare authentic samples of $\mathbf{41_{Ar}}$.

when solvated by DMA; collaborative efforts have recently begun to further probe the mechanism of this transformation.

Experimental

General considerations

Dry dimethylacetamide (DMA) was purchased from Aldrich and stored over activated 3 Å molecular sieves (3 Å MS). Terminal olefins were purchased from Aldrich, TCI or Acros, or synthesized according to the procedures referenced. Aniline precursors to aryldiazonium tetrafluoroborates were purchases from Aldrich. Palladium(II) chloride was purchased from Pressure Chemicals. (*S*)-1-Octene-3-ol was purchased from Fluka. Pd_2dba_3 was synthesized according to the literature procedure.[55] I^{i}Pr carbene was synthesized according to the literature procedure.[56] ^{1}H-NMR spectra were obtained at 300 MHz or 400 MHz, chemical shifts are reported in ppm, and referenced to the $CHCl_3$ singlet at 7.26 ppm. ^{13}C-NMR spectra were obtained at 75 MHz or 100 MHz and referenced to the center peak of the $CDCl_3$ triplet at 77.23 ppm. The abbreviations s, d, t, quint, dd, dt, m stand for the resonance multiplicities singlet, doublet, triplet, quintet, doublet of doublets, doublet of triplets, and multiplet, respectively. Thin-layer chromatography was performed with EMD silica gel 60 F254 plates eluting with the solvents indicated, visualized by a 254 nm UV lamp, and stained with phosphomolybdic

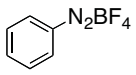
acid. Flash chromatography was performed using EM reagent silica 60 (230-400 mesh). IR spectra were recorded using a Thermo Nicolet FT-IR. HRMS data were obtained on a Waters LCP Premier XE instrument by ESI/TOF. Achiral GC (gas chromatography) was performed using a Hewlett Packard HP 6890 series GC system fitted with an Agilent HP-5 column. Chiral GC analysis was performed using a Hewlett Packard HP 6890 Series GC system fitted with a HP-Chiral permethylated β-cyclodextrin column. SFC (supercritical fluid chromatography) analysis was performed at 40 ºC, using a Thar instrument fitted with an AD-H column. It should be noted that while no incident occurred during this study, aryldiazonium salts can be explosive. It is also important to note that these reactions should be monitored carefully, as the products decompose under the reaction conditions.

Synthesis of alkene substrates

tert-Butyldimethyl((1-phenylbut-3-en-1-yl)oxy)silane,[57] 1-phenylbut-3-en-1-ol,[57] oct-1-en-3-yl acetate,[58] and 4-vinylphenol[59] were prepared following literature procedures and purity confirmed via ^{1}H NMR. *N*-Cbz-*N*-Boc-Allylamine was prepared following the literature procedure,[60] and its purity confirmed via ^{1}H NMR.[61] (*S*)-1-Octene-3-ol (**33**) was converted to oct-1-en-3-yl acetate using the same procedure as that used to synthesize the corresponding racemic substrate. The enantiomeric excess of the resulting acetate protected alcohol was determined by GC equipped with a chiral column (see below).

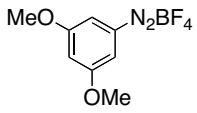
Synthesis of aryldiazonium tetrafluoroborate salts

Benzenediazonium tetrafluoroborate



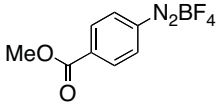
Benzenediazonium tetrafluoroborate was synthesized according to a previously reported procedure[62] and the ^{1}H NMR spectrum was compared to the previously reported spectrum.[63]

3,5-Dimethoxybenzenediazonium tetrafluoroborate



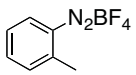
3,5-Dimethoxybenzenediazonium tetrafluoroborate was synthesized according to a previously reported procedure[62] and the ^{1}H NMR spectrum was compared to the previously reported spectrum.[64]

4-Methoxycarbonylbenzenediazonium tetrafluoroborate



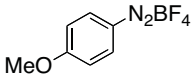
4-Methoxycarbonylbenzenediazonium tetrafluoroborate was synthesized according to a previously reported procedure[62] and the ^{1}H NMR spectrum was compared to the previously reported spectrum.[65]

2-Methylbenzenediazonium tetrafluoroborate



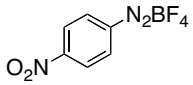
2-Methylbenzenediazonium tetrafluoroborate was synthesized according to a previously reported procedure[62] and the ^{1}H NMR spectrum was compared to the previously reported spectrum.[66]

4-Methoxybenzenediazonium tetrafluoroborate



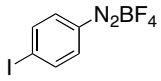
4-Methoxybenzenediazonium tetrafluoroborate was synthesized according to a previously reported procedure[62] and the ^{1}H NMR spectrum was compared to the previously reported spectrum.[65]

4-Nitrobenzenediazonium tetrafluoroborate



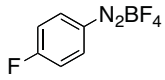
4-Nitrobenzenediazonium tetrafluoroborate was synthesized according to a previously reported procedure[62] and the ^{1}H NMR spectrum was compared to the previously reported spectrum.[63]

4-Iodobenzenediazonium tetrafluoroborate



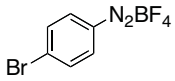
4-Iodobenzenediazonium tetrafluoroborate was synthesized according to a previously reported procedure[62] and the ^{1}H NMR spectrum was compared to the previously reported spectrum.[67]

4-Fluorobenzenediazonium tetrafluoroborate



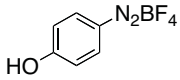
4-Fluorobenzenediazonium tetrafluoroborate was synthesized according to a previously reported procedure[62] and the ^{1}H NMR spectrum was compared to the previously reported spectrum.[65]

4-Bromobenzenediazonium tetrafluoroborate



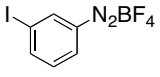
4-Bromobenzenediazonium tetrafluoroborate was synthesized according to a previously reported procedure[62] and the ^{1}H NMR spectrum was compared to the previously reported spectrum.[67]

4-Hydroxybenzenediazonium tetrafluoroborate



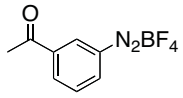
4-Hydroxybenzenediazonium tetrafluoroborate was synthesized according to a previously reported procedure[68] and the ^{1}H NMR spectrum was compared to the previously reported spectrum.[68]

3-Iodobenzenediazonium tetrafluoroborate



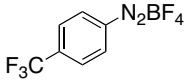
3-Iodobenzenediazonium tetrafluoroborate was synthesized according to a previously reported procedure[62] and the ^{1}H NMR spectrum was compared to the previously reported spectrum.[69]

3-Acetylbenzenediazonium tetrafluoroborate



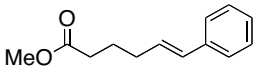
3-Acetylbenzenediazonium tetrafluoroborate was synthesized according to a previously reported procedure[62] and the ^{1}H NMR spectrum was compared to the previously reported spectrum.[70]

4-Trifluoromethylbenzenediazonium tetrafluoroborate



4-Trifluoromethylbenzenediazonium tetrafluoroborate was synthesized according to a previously reported procedure[62] and the ^{1}H NMR spectrum was compared to the previously reported spectrum.[71]

Procedure for the synthesis of (*E*)-methyl 6-phenylhex-5-enoate (**12**)
under initial conditions (Table 3.1, entry 1)



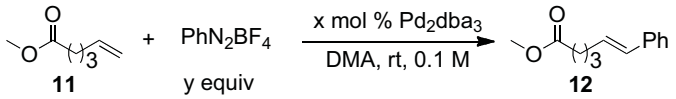
In the dry box, an oven-dried 25 mL round bottomed flask equipped with a stir bar was charged with 58 mg benzenediazonium tetrafluoroborate (0.3 mmol, 1.5 equiv). To a separate vial equipped with a stir bar was added 9 mg Pd_2dba_3 (0.01 mmol, 0.05

equiv), 10 mg I^iPr carbene (0.03 mmol, 0.125 equiv) and 1 mL DMA, and the mixture was stirred for 10 minutes. To a separate vial was added 26 mg methyl hex-5-enoate (**11**) (0.2 mmol) and 1 mL DMA. To the flask containing the areyldiazonium salt was added the solution containing **11**, followed quickly by the solution containing Pd_2dba_3 and I^iPr carbene. The flask was fitted with a septum, removed from the dry box, and stirred for 16 h. The mixture was diluted with 10 mL Et_2O and transferred to a separatory funnel. To this, 15 mL of distilled water were added, and the aqueous layer was extracted twice with 10 mL Et_2O. The combined organic extracts were washed three times with 15 mL distilled water, then 15 mL brine, followed by drying over Na_2SO_4. The mixture was filtered and the solvent was removed in vacuo. This material was purified by silica gel flash chromatography eluting with 1% acetone in hexanes, and a mixture containing **12** and decomposition products was obtained.

Optimization of the Heck reaction

The procedure for the preparation of **12** described above was used with the following modifications. The reaction was performed using ~10 wt% (to **11**) tetradecane as an internal standard. After either 16 h or 15 min (see Table 3.1) aliquots (~50 μL) were removed, passed through a small silica pipet with ether, and analyzed for conversion, product formation, and selectivity by gas chromatography. The modifications described in Table 3.1 were applied in order to optimize the reaction.

Table 3.1. Optimization of classical Heck reactions.



11 y equiv **12**

entry	x	y	time	% conversion[a]	% yield[a]	selectivity[b]
1[c]	5	1.5	16 h	>99	68.4	3.8:1
2	5	1.5	16 h	>99	43.3	6.8:1
3	5	1.5	15 min	>99	62.6	7.1:1
4	3	1.5	15 min	>99	86.2	7.5:1
5	3	1.1	15 min	>99	>99	10.7:1
6	0	1.1	15 min	3.6	0	-

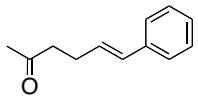
[a]Conversion and yield were calculated by comparing starting material and product peak integration to integration of internal standard using corrected GC analysis. Yield refers to the sum of all product isomers [b]Selectivity refers to the ratio of (*E*)-styrene to the sum of all other isomers. [c]12.5 mol % I^{i}Pr carbene added.

General procedure for the preparation of **12** under optimized conditions (Table 3.2, entry 1)

In the dry box, an oven dried 25 mL round-bottom flask equipped with a stir bar was charged with 106 mg benzenediazonium tetrafluoroborate (0.55 mmol, 1.1 equiv). To a separate vial was added 14 mg Pd_2dba_3 (0.02 mmol, 0.03 equiv) and 3 mL DMA. To a separate vial was added 64 mg **11** (0.5 mmol) and 2 mL DMA. To the flask containing the arenediazonium salt was added the solution containing **11**, followed quickly by the solution containing Pd_2dba_3. The flask was fitted with a septum, quickly removed from the dry box, and stirred for 20 min. The mixture was diluted with 20 mL Et_2O and transferred to a separatory funnel. To this, 20 mL of distilled water were added, and the aqueous layer was extracted twice with 20 mL Et_2O. The combined organic extracts were washed three times with 15 mL distilled water then 15 mL brine followed by drying over Na_2SO_4. The mixture was filtered and the solvent was removed in vacuo. The product was purified by silica gel flash chromatography eluting with 1% acetone in

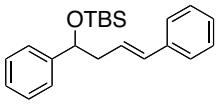
hexanes and was isolated as a clear oil in 95-99% yield (97 mg and 101 mg)**.** The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[72]

Table 3.2, entry 2 ((*E*)-6-phenylhex-5-en-2-one) (**13**)



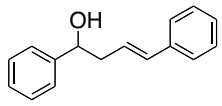
The general procedure for the preparation of **12** was used with the modifications that 49 mg hex-5-en-2-one (0.50 mmol) and 106 mg benzenediazonium tetrafluoroborate (0.55 mmol, 1.1 equiv) were used, and the mixture was stirred for 20 min before workup. The product was purified by silica gel flash chromatography by eluting with 2% acetone in hexanes to give **13** as a clear oil in 88-90% yield (77 and 78 mg). The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[72]

Table 3.2, entry 3 ((*E*)-*tert*-butyl((1,4-diphenylbut-3-en-1-yl)oxy)dimethylsilane) (**14**)



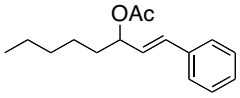
The general procedure for the preparation of **12** was used with the modifications that 131 mg *tert*-butyldimethyl((1-phenylbut-3-en-1-yl)oxy)silane (0.50 mmol) and 106 mg benzenediazonium tetrafluoroborate (0.55 mmol, 1.1 equiv) were used, and the mixture was stirred for 16 h before workup. The product was purified by silica gel flash chromatography by eluting with 1% acetone in hexanes to give **14** as a clear oil in 87% yield (145 and 144 mg). The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[72]

Table 3.2, entry 4 ((*E*)-1,4-diphenylbut-3-en-1-ol (**15**)



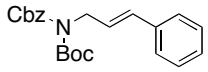
The general procedure for the preparation of **12** was used with the modifications that 74 mg 1-phenylbut-3-en-1-ol (0.50 mmol) and 106 mg benzenediazonium tetrafluoroborate (0.55 mmol, 1.1 equiv) were used, and the mixture was stirred for 1.5 h before workup. The product was purified by silica gel flash chromatography by eluting with 10% acetone in hexanes to give **15** as a white solid in 67-75% yield (75 and 84 mg). The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[72]

Table 3.2, entry 5 (*E*)-1-phenyloct-1-en-3-yl acetate (**16**)



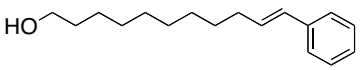
The general procedure for the preparation of **12** was used with the modifications that 23 mg Pd_2dba_3 (0.03 mmol, 0.05 equiv), 85 mg oct-1-en-3-yl acetate (0.50 mmol) and 144 mg benzenediazonium tetrafluoroborate (0.75 mmol, 1.5 equiv) were used, and the mixture was stirred for 16 h before workup. The product was purified by silica gel flash chromatography by eluting with 2% acetone in hexanes to give **16** as a clear oil in 85-88% yield (105 and 108 mg). The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[72]

Table 3.2, entry 6 ((*E*)-*N*-Cbz-*N*-Boc-3-phenylprop-2-en-1-amine) (**17**)



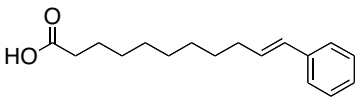
The general procedure for the preparation of **12** was used with the modifications that 87 mg *N*-Cbz-*N*-Boc-prop-2-en-1-amine (0.30 mmol) and 86 mg benzenediazonium tetrafluoroborate (0.45 mmol, 1.5 equiv) were used in 3.0 mL DMA, and the mixture was stirred for 16 h before workup. The product was purified by silica gel flash chromatography by eluting with 2% acetone in hexanes to give **17** as a white solid in 96% yield (105 and 106 mg). The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[72]

Table 3.2, entry 7 ((*E*)-11-phenylundec-10-en-1-ol) (**18**)



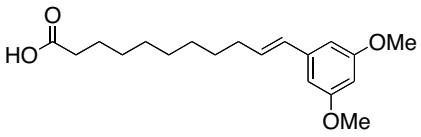
The general procedure for the preparation of **12** was used with the modifications that 85 mg undec-10-en-1-ol (0.50 mmol) and 106 mg benzenediazonium tetrafluoroborate (0.55 mmol, 1.1 equiv) were used, and the mixture was stirred for 40 min before workup. The product was purified by silica gel flash chromatography by eluting with 5% acetone in hexanes to give **18** as a white solid in 75-79% yield (93 and 97 mg). The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[72]

Table 3.2, entry 8 ((*E*)-11-phenylundec-10-enoic acid (**19**)



The general procedure for the preparation of **12** was used with the modifications that 92 mg undec-10-enoic acid (0.50 mmol) and 106 mg benzenediazonium tetrafluoroborate (0.55 mmol, 1.1 equiv) were used, and the mixture was stirred for 2 h before workup. The product was purified by silica gel flash chromatography by eluting with 5% acetone in hexanes to give **19** as a clear oil in 94-96% yield (122 and 125 mg). R_f = 0.26 w/ 15% acetone in hexanes. IR (neat): 3024, 2924, 2853, 1704, 1494, 1411, 1284, 1239, 963, 743, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.49-1.26 (m, 10 H), 1.66-1.59 (m, 2 H), 2.19 (dt, *J* = 7.0, 6.7 Hz, 2 H), 2.35 (t, *J* = 7.4 Hz, 2 H), 6.22 (dt, *J* = 15.9, 6.7 Hz, 1 H) 6.38 (d, *J* = 15.9 Hz, 1 H) 7.36-7.16 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8, 29.2, 29.3, 29.4, 29.5, 29.5, 33.2, 34.3, 126.1, 126.9, 128.6, 129.9, 131.3, 138.1, 180.8. HRMS $C_{17}H_{24}O_2$ $(M+Na)^+$ calcd.; 283.1674 obsd.; 283.1675.

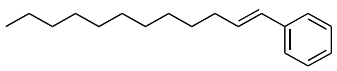
Table 3.2, entry 9 ((*E*)-(3,5-dimethoxyphenyl)undec-10-enoic acid (**20**)



The general procedure for the preparation of **12** was used with the modifications that 92 mg undec-10-enoic acid (0.50 mmol) and 139 mg 3,5-dimethoxyphenyldiazonium tetrafluoroborate (0.55 mmol, 1.1 equiv) were used, and the mixture was stirred for 2 h before workup. The product was purified by silica gel flash chromatography by eluting with 10% acetone in hexanes to give **20** as a white solid (MP = 45-47 ^oC) in 67-71% yield (108 and 113 mg). R_f = 0.18 w/ 15% acetone in hexanes. IR (neat): 2967, 2853, 1707, 1592, 1458, 1425, 1293, 1204, 1152, 1065, 965, 927, 827, 683, 668 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.49-1.25 (m, 10 H), 1.69-1.57 (m, 2 H), 2.19 (dt, *J* = 7.5, 6.9 Hz, 2

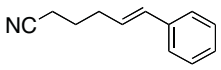
H), 2.35 (t, J = 7.4 Hz, 2 H), 3.79 (s, 6 H), 6.34-6.15 (m, 3 H), 6.51 (d, J = 2.2 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8, 29.2, 29.3, 29.4, 29.5, 29.5, 33.1, 34.3, 55.9, 99.3, 104.2, 129.9, 132.0, 140.2, 161.0, 180.4. HRMS $C_{19}H_{28}O_4$ $(M+Na)^+$ calcd.; 343.1885 obsd.; 343.1880.

Table 3.2, entry 10 ((*E*)-docec-1-en-1-ylbenzene) (**21**)



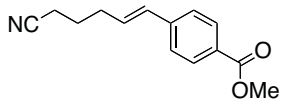
The general procedure for the preparation of **12** was used with the modifications that 84 mg 1-dodecene (0.50 mmol) and 106 mg benzenediazonium tetrafluoroborate (0.55 mmol, 1.1 equiv) were used, and the mixture was stirred for 20 min before workup. The product was purified by silica gel flash chromatography by eluting with 5% acetone in hexanes to give **21** as a clear oil in 77% yield (94 and 93 mg). The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[73]

Table 3.2, entry 11 ((*E*)-6-phenylhex-5-enenitrile) (**22**)



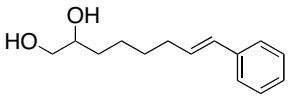
The general procedure for the preparation of **21** was used with the modifications that 48 mg hex-5-enenitrile (0.50 mmol) and 106 mg benzenediazonium tetrafluoroborate (0.55 mmol, 1.1 equiv) were used, and the mixture was stirred for 3 h before workup. The product was purified by silica gel flash chromatography by eluting with 5% acetone in hexanes to give **22** as a clear oil in 96% yield (82 and 81 mg). The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[74]

Table 3.2, entry 12 ((*E*)-methyl 4-(5-cyanopent-1-en-1-yl)benzoate) (**23**)



The general procedure for the preparation of **12** was used with the modifications that 48 mg hex-5-enenitrile (0.50 mmol) and 138 mg 4-methoxycarbonyl benzenediazonium tetrafluoroborate (0.55 mmol, 1.1 equiv) were used, and the mixture was stirred for 3 h before workup. The product was purified by silica gel flash chromatography by eluting with 10% acetone in hexanes to give **23** as a white solid (MP = 49-50 ^{o}C) in 96-99% yield (110 and 113 mg). R_f = 0.11 w/ 5% acetone in hexanes. IR (neat): 1951, 2246, 1713, 1650, 1605, 1434, 1413, 1274, 1177, 1107, 1016, 961, 872, 761 697 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.87 (quint, *J* = 7.2, 2 H), 2.46-2.39 (m, 4 H), 3.90 (s, 3 H), 6.27 (dt, *J* = 15.8, 7.0 Hz, 1 H), 6.50 (d, *J* = 15.9 Hz, 1 H), 7.55 (d, *J* = 8.2 Hz, 2 H), 7.97 (d, *J* = 8.3 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.7, 24.9, 31.9, 52.2, 119.6, 126.1, 128.9, 130.1, 130.7, 131.3, 141.7, 167.0. HRMS $C_{14}H_{15}NO_2$ $(M+Na)^+$ calcd.; 252.1000 obsd.; 252.0986.

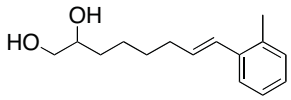
Table 3.2, entry 13 ((*E*)-8-phenyloct-7-ene-1,2-diol) (**24**)



The general procedure for the preparation of **12** was used with the modifications that 72 mg oct-7-ene-1,2-diol (0.50 mmol) and 106 mg benzenediazonium tetrafluoroborate (0.55 mmol, 1.1 equiv) were used, and the mixture was stirred for 2 h before workup. The product was purified by silica gel flash chromatography by eluting with 20% acetone in hexanes to give **24** as a white solid (MP = 44-46 ^{o}C) in 81-84%

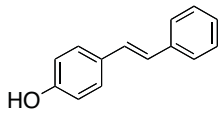
yield (89 and 93 mg). R_f = 0.05 w/ 15% acetone in hexanes. IR (neat): 3343, 3057, 3024, 2929, 2856, 1598, 1493, 1447, 1070, 963, 864, 744, 693, 668 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.54-1.47 (m, 6 H) 1.88 (br s, 1 H), 2.03 (br s, 1 H), 2.27- 2.20 (m, 2 H) 3.47-3.41 (m, 1 H) 3.74-3.66 (m, 2 H), 6.21 (dt, *J* = 15.8, 6.8 Hz, 1 H), 6.33 (d, *J* = 15.9 Hz, 1 H), 7.44-7.17 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.3, 29.5, 33.1, 33.2, 67.0, 72.4, 126.1, 127.0, 128.7, 130.2, 130.9, 137.9. HRMS $C_{14}H_{20}O_2$ $(M+Na)^+$ calcd.; 243.1361 obsd.; 243.1355.

Table 3.2, entry 14 ((*E*)-8-(*o*-tolyl)oct-7-ene-1,2-diol (**25**)



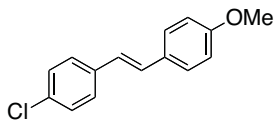
The general procedure for the preparation of **12** was used with the modifications that 23 mg Pd_2dba_3 (0.03 mmol, 0.05 equiv), 72 mg oct-7-ene-1,2-diol (0.50 mmol) and 155 mg 2-methylbenzenediazonium tetrafluoroborate (0.75 mmol, 1.5 equiv) were used, and the mixture was stirred for 2 h before workup. The product was purified by silica gel flash chromatography by eluting with 20% acetone in hexanes to give **25** as a clear oil in 66% yield (76 and 77 mg). R_f = 0.07 w/ 15% acetone in hexanes. IR (neat): 3350, 3020, 2930, 2857, 1652, 1601, 1484, 1460, 1101, 1053, 964, 866, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.58-1.44 (m, 6 H), 1.90-1.80 (m, 1 H), 2.04-1.99 (m, 1 H), 2.30-2.22 (m, 2 H), 2.33 (s, 3 H), 3.49-3.40 (m, 1 H), 3.75-3.65 (m, 2 H), 6.08 (dt, *J* = 15.7, 6.9 Hz, 1 H), 6.57 (d, *J* = 15.5 Hz, 1 H), 7.21-7.10 (m, 3 H), 7.40 (d, *J* = 5.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.0, 25.3, 29.6, 33.1, 33.4, 67.0, 72.4, 125.6, 126.2, 127.0, 128.0, 130.3, 132.2, 135.0, 137.1. HRMS $C_{15}H_{22}O_2$ $(M+Na)^+$ calcd.; 257.1517 obsd.; 257.1505.

Table 3.2, entry 15 ((*E*)-4-styrylphenol (**26**)



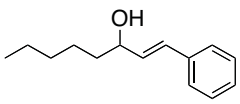
The general procedure for the preparation of **12** was used with the modifications that 60 mg 4-vinylphenol (0.50 mmol) and 106 mg benzenediazonium tetrafluoroborate (0.55 mmol, 1.1 equiv) were used, and the mixture was stirred for 1.5 h before workup. The product was purified by silica gel flash chromatography by eluting with 10% acetone in hexanes to give **26** as a white solid in 97-99% yield (95 and 97 mg). The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[75]

Table 3.2, entry 16 ((*E*)-1-chloro-4-(4-methoxystyryl)benzene (**27**)



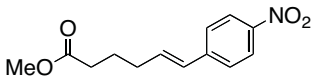
The general procedure for the preparation of **12** was used with the modifications that 69 mg 1-chloro-4-vinylbenzene (0.50 mmol) and 122 mg 4-methoxybenzendiazonium tetrafluoroborate (0.55 mmol, 1.1 equiv) were used, and the mixture was stirred for 1.5 h before workup. The product was purified by silica gel flash chromatography by eluting with 3% acetone in hexanes to give **27** as a white solid in 96-99% yield (117 and 121 mg). The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[76]

Table 3.2, entry 17 ((*E*)-1-phenyloct-1-en-3-ol) (**28**)



The general procedure for the preparation of **12** was used with the modifications that 23 mg Pd_2dba_3 (0.03 mmol, 0.05 equiv), 64 mg oct-1-en-3-ol (0.50 mmol) and 144 mg benzenediazonium tetrafluoroborate (0.75 mmol, 1.5 equiv) were used, and the mixture was stirred for 16 h before workup. The product was purified by silica gel flash chromatography by eluting with 5% acetone in hexanes to give **28** as a clear oil in 52-57% yield (53 and 58 mg). R_f = 0.18 w/ 5% acetone in hexanes. IR (neat): 3338, 3060, 3026, 2955, 2928, 2857, 1599, 1494, 1449, 1132, 1027, 965, 748, 692 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.8 Hz, 3 H), 1.43-1.26 (m, 6 H), 1.68-1.57 (m, 3 H), 4.32-4.24 (m, 1 H), 6.22 (dd, *J* = 15.9, 6.8 Hz, 1 H), 6.55 (d, *J* = 15.9 Hz, 1 H), 7.40-7.22 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 22.8, 25.4, 32.0, 73.4, 126.7, 127.8, 128.8, 130.4, 132.8, 136.9. HRMS $C_{14}H_{20}O$ $(M)^+$ calcd.; 205.1592 obsd.; 205.1582.

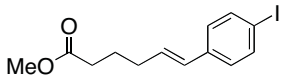
Table 3.2, entry 18 ((*E*)-methyl-6-(4-nitrophenyl)hex-5-enoate (**29**)



The general procedure for the preparation of **12** was used with the modifications that 64 mg methyl 5-hexenoate (0.50 mmol) and 130 mg 4-nitrobenzenediazonium tetrafluoroborate (0.55 mmol, 1.1 equiv) were used, and the mixture was stirred for 20 minutes before workup. The product was purified by silica gel flash chromatography by eluting with 10% acetone in hexanes to give **29** as a clear oil in 96-99% yield (119 and 122 mg). Note: when submitting slower reacting substrates (or allowing this reaction to proceed longer than 20 min) to the Heck reaction with 4-nitrobenzenediazonium tetrafluoroborate we observed decomposition of the desired product likely due to the highly reactive nitrostyrene product. R_f = 0.21 w/ 5% acetone in hexanes. IR (neat): 2947,

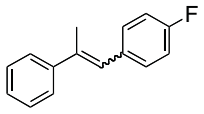
1731, 1483, 1435, 1397, 1243, 1196, 1151, 1061, 1003, 966, 842, 797 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.81 (quint, *J* = 7.6 Hz, 2 H), 2.24 (dt, *J* = 7.6, 7.4 Hz, 2 H), 2.39 (t, *J* = 7.5 Hz, 2 H), 3.66 (s, 3 H), 6.18 (dt, *J* = 15.8, 6.6 Hz, 1 H), 6.31 (d, *J* = 15.9 Hz, 1 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 7.61 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.2, 32.6, 33.5, 51.8, 124.1, 126.6, 129.2, 135.1, 144.2, 146.7, 173.9. HRMS $C_{13}H_{15}NO_4$ $(M+Na)^+$ calcd.; 272.0899 obsd.; 272.0893.

Table 3.2, entry 19 ((*E*)-methyl-6-(4-iodophenyl)hex-5-enoate (**30**)



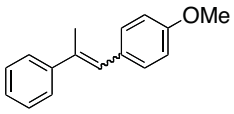
The general procedure for the preparation of **12** was used with the modifications that 64 mg methyl 5-hexenoate (0.50 mmol) and 159 mg 4-iodobenzenediazonium tetrafluoroborate (0.55 mmol, 1.1 equiv) were used, and the mixture was stirred for 20 min before workup. The product was purified by silica gel flash chromatography by eluting with 2% acetone in hexanes to give **30** as a clear oil in 60-74% yield (99, 122, 107 mg). R_f = 0.40 w/ 5% acetone in hexanes. IR (neat): 2950, 1734, 1596 1515, 1436, 1342, 1180, 1109, 971, 858, 744, 691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.85 (quint, *J* = 7.2 Hz, 2 H), 2.41-2.28 (m, 4 H), 3.67 (s, 3 H), 6.50-6.34 (m, 2 H), 7.45 (d, *J* = 8.9 Hz, 2 H), 8.16 (d, *J* = 9.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5, 32.5, 33.5, 51.7, 92.2, 128.0, 130.0, 130.7, 137.2, 137.7, 174.1. HRMS $C_{13}H_{15}IO_4$ $(M+Na)^+$ calcd.; 353.0015 obsd.; 353.0012.

Table 3.2, entry 20 (1-fluoro-4-(2-phenylprop-1-en-1-yl)benzene) (**31**)



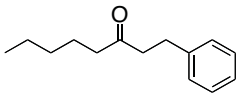
The general procedure for the preparation of **12** was used with the modifications that 23 mg Pd_2dba_3 (0.03 mmol, 0.05 equiv), 59 mg α-methylstyrene (0.50 mmol) and 157 mg 4-fluorobenzenediazonium tetrafluoroborate (0.75 mmol, 151 equiv) were used, and the mixture was stirred for 2 h before workup. The product was purified by silica gel flash chromatography by eluting with 1% acetone in hexanes to give **31** as a white solid in 99% yield (105 and 105 mg). The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[77]

Table 3.2, entry 21 (1-methoxy-4-(2-phenylprop-1-en-1-yl)benzene) (**32**)



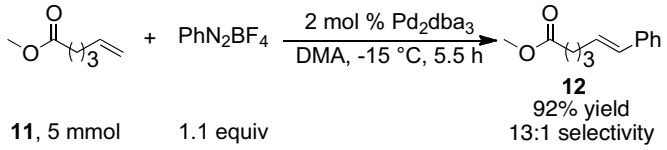
The general procedure for the preparation of **12** was used with the modifications that 23 mg Pd_2dba_3 (0.03 mmol, 0.05 equiv), 59 mg α-methylstyrene (0.50 mmol) and 167 mg 4-methoxybenzenediazonium tetrafluoroborate (0.75 mmol, 151 equiv) were used, and the mixture was stirred for 2 h before workup. The product was purified by silica gel flash chromatography by eluting with 3% acetone in hexanes to give **32** as a white solid in 99% yield (111 and 110 mg). The ^{1}H NMR spectrum, see below, was compared with the previously reported spectrum.[78]

Figure 3.17 (1-phenyloctane-3-one) (**34**)



1-Phenyloctane-3-one (**34**) was isolated as a clear oil in 41-46% yield as a byproduct of the reaction used to prepare **28** (42 and 47 mg). R_f = 0.41 w/ 5% acetone in hexanes. IR (neat): 3027, 2955, 2929, 2859, 1713, 1604, 1496, 1454, 1409, 1371, 1126, 1080, 748, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.1 Hz, 3 H) 1.35-1.19 (m, 4 H), 1.56 (quint, *J* = 7.3 Hz, 2 H), 2.38 (t, *J* = 7.3 Hz, 2 H), 2.73, (t, *J* = 7.5 Hz, 2 H), 2.90 (t, *J* = 7.3 Hz, 2 H) 7.20-7.17 (m, 3 H), 7.30-7.26 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 23.7, 30.0, 31.6, 43.2, 44.5, 126.7, 128.5, 128.7, 141.4, 210.6. HRMS $C_{14}H_{20}O$ $(M+Na)^+$ calcd.; 227.1412 obsd.; 227.1408.

Figure 3.18, procedure for the preparation of **12** on 5 mmol scale



In the dry box, an oven dried 250 mL round bottomed flask equipped with a stir bar was charged with 1.06 g benzenediazonium tetrafluoroborate (5.5 mmol, 1.1 equiv). To an oven dried 100 mL round bottomed flask with a stir bar was added 92 mg Pd_2dba_3 (0.1 mmol, 0.02 equiv), 641 mg methyl 5-hexenoate (**11**) (5 mmol) and 50 mL DMA. The flasks were fitted with septa, removed from the dry box, and placed in an ice/acetone bath. After cooling for 20 min, the solution containing **11** and the catalyst was cannulated into the flask containing phenyldiazonium tetrafluoroborate. The mixture was stirred in the cold bath, and starting material consumption was monitored by TLC. After 5.5 h the

mixture was diluted with 50 mL Et_2O and transferred to a separatory funnel. To this, 50 mL of distilled water were added, and the aqueous layer was extracted twice with 50 mL Et_2O. The combined organic extracts were washed four times with 50 mL distilled water and then 50 mL brine followed by drying over Na_2SO_4. The mixture was filtered and the solvent was removed in vacuo. The product was purified by silica gel flash chromatography eluting with 1% acetone in hexanes and **12** was isolated as a clear oil in 92% yield (943 mg).

Unsuccessful reactions

Figure 3.19, unsuccessful preparation of aryldiazonium tetrafluoroborates

Attempts to prepare aryldiazonium tetrafluoroborate salts bearing an *o*-phenol, an acetamide, or 2,6-dimethyl groups using the general procedure for the preparation of aryldiazonium salts were unsuccessful.

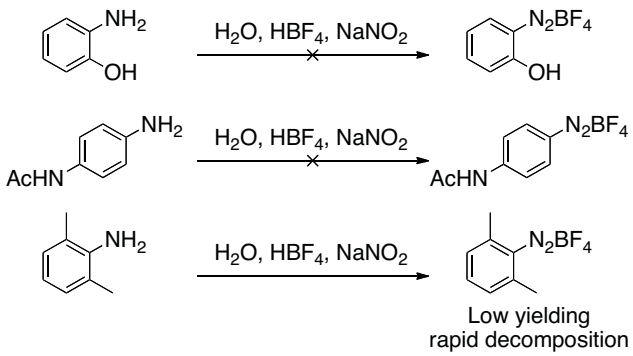


Figure 3.20, unsuccessful Heck reactions

Submission of the following alkenes to the general procedure to synthesize **12** led to complex mixtures, did not result the in isolation of any desired product, or led to the isolation of starting material.

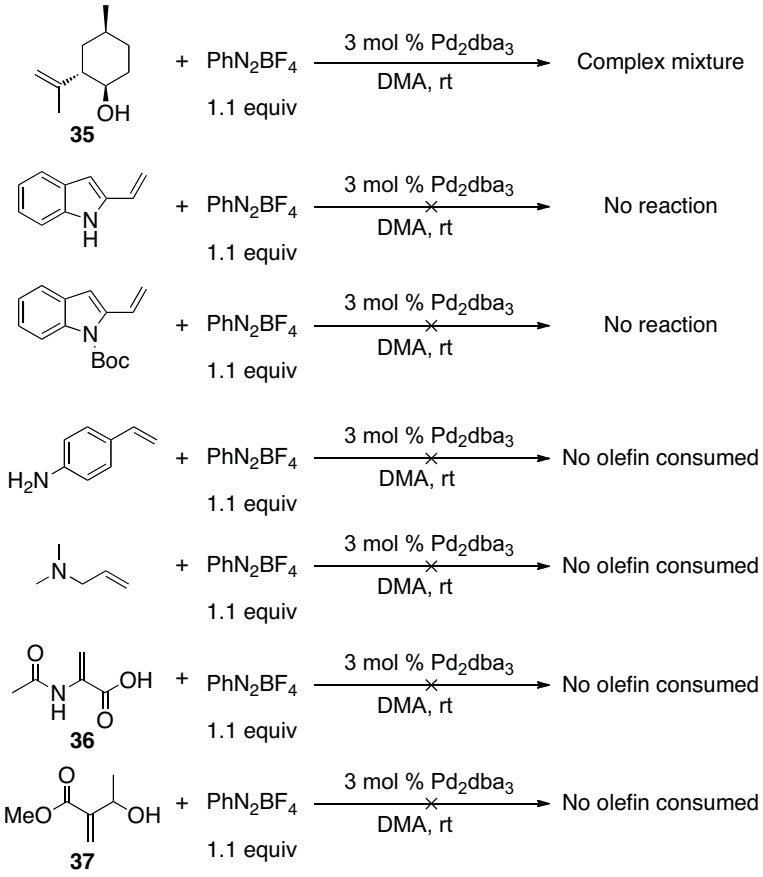


Figure 3.21, unsuccessful use of aryldiazonium tetrafluoroborates

Submission of the following aryldiazonium tetrafluoroborates to the general procedure to synthesize **12** led to the isolation of starting material.

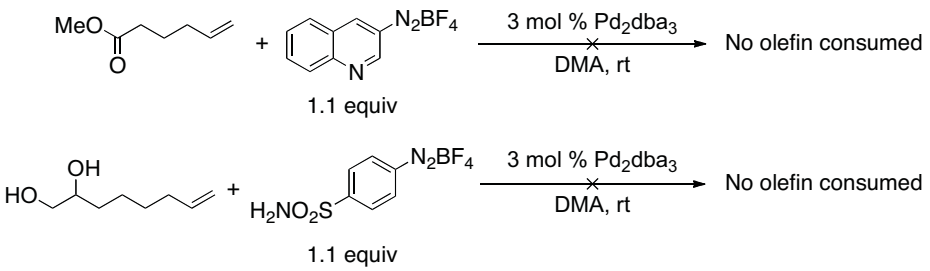
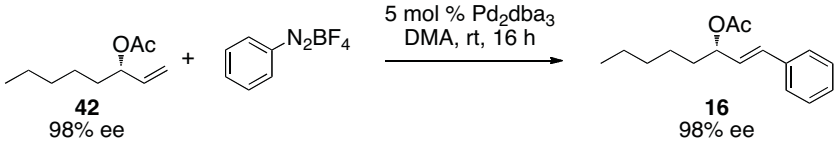


Table 3.2, entry 22, evaluation of retention of enantiomeric excess



The same procedure used to synthesize racemic **16** was used except 34 mg (*S*)-oct-1-en-3-yl acetate (**42**) was added, and the product was purified after 16 h by silica gel chromatography by eluting with 1% acetone in hexanes. The purified product was evaluated for enantiomeric excess using chiral SFC (see below).

compound	method	retention times (min)
42	GC hold 100 °C 25 min	2.7 and 2.9
16	SFC 1% MeOH 2 mL/min	4.3 and 5.5

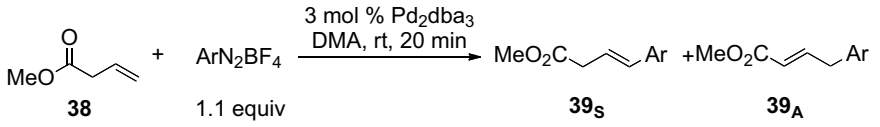
Table 3.3, comparison of results of Pd^0 conditions commonly used for Heck reactions

The general procedure for the preparation of **12** was used with the following modifications (see Table 3.3). The reaction was performed on 0.2 mmol scale (w/10 wt% tetradecane as internal standard) using the oxidant and solvent described below. The mixture was stirred at room temperature, and small aliquots (~50 μL) were removed,

passed through a small silica pipet with ether, and analyzed for conversion, product formation, and selectivity by gas chromatography. For entries 1, 4 and 5 a similar reaction was performed, omitting tetradecane, and was worked up in the fashion described above after 1 h, the solutions were concentrated, and the crude mixtures were analyzed by ^{1}H NMR.

Construction of Hammett plot

Figure 3.22, results using β,γ-unsaturated ester (**38**)

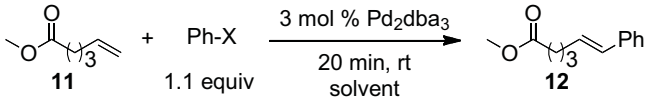


38 1.1 equiv **39S** **39A**

Ar	**39S/39A**	Ar	**39S/39A**
4-H	6.03	4-CO_2Me	7.69
4-NO_2	6.11	4-Br	6.47
4-OMe	7.87	4-F	6.12

The general procedure for the preparation of **12** was used with the modifications that 20 mg methyl but-3-enoate **38** (0.20 mmol) and various aryldiazonium tetrafluoroborate salts (0.22 mmol, 1.1 equiv) were used, and the mixtures were stirred

Table 3.3. Comparison of the results observed under more frequently used conditions in classical Heck reactions



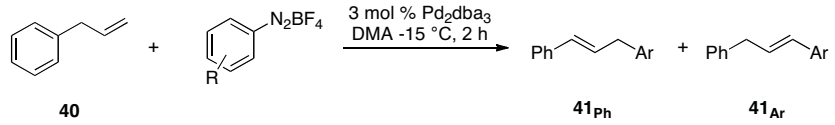
11 1.1 equiv **12**

entry	x	solvent	% conversion[a]	% yield[a]	selectivity[b]
1	N_2BF_4	DMA	>99	>99	10.7:1
2[c]	I	DMA	2.5	1.0	1.6:1
3[c]	OTs	DMA	<1	0.1	1.2:1
4	N_2BF_4	MeOH	>99	20	0.2:1
5	N_2BF_4	MeCN	98.1	15	0.3:1

[a]Conversion and yield calculated by comparing starting material and product peak integration to integration of internal standard using GC analysis. [b]Selectivity is (*E*)-styrene:all other isomers. [c]Reaction allowed to stir for 1 h.

for 20 min before workup. Following concentration in vacuo, the mixtures were analyzed by ^{1}H NMR to determine the ratio of $\mathbf{39_A}$:$\mathbf{39_S}$ by comparing the integration of the vinyl or allylic protons of each product.

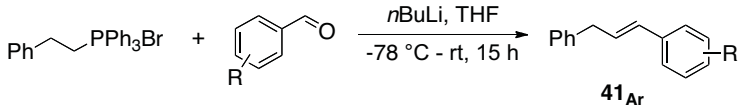
Figure 3.23 b, results using allyl benzene (**40**)



40 $\mathbf{41_{Ph}}$ $\mathbf{41_{Ar}}$

The general procedure for the preparation of **12** was used with the modifications that 5 mg Pd_2dba_3, 24 mg allyl benzene (**40**) (0.2 mmol), and various aryldiazonium tetrafluoroborate salts (0.22 mmol, 1.1 equiv) were used. The mixtures were stirred at -15 ^{o}C (using an ice/acetone bath) for 2 h before workup. The reactions were cooled because these Heck reactions are exothermic, and results were more consistent when using a heat sink. The crude mixtures were analyzed by a combination of ^{1}H NMR (comparing the integration of the allylic protons of each compound to determine which isomer was major) and GC (to accurately determine the ratio of $\mathbf{41_{Ph}}$:$\mathbf{41_{Ar}}$. In addition, authentic samples of $\mathbf{41_{Ar}}$ were prepared using the procedure described below to ensure the correct identification of each isomer.

Figure 3.24, general procedure for the synthesis of authentic samples of $\mathbf{41_{Ar}}$



$\mathbf{41_{Ar}}$

Wittig reactions, performed based on a previously reported procedure,[79] were used to synthesize authentic samples of **41$_{Ar}$**. To oven dried 50 mL round bottomed flasks equipped with stir bars was added 671 mg bromo(phenethyl)triphenylphosphorane (1.5 mmol, 1.5 equiv). The flasks were fitted with reflux condensers, and placed under nitrogen. Tetrahydrofuran (THF) (5 mL) was added, followed by *n*-butyllithium (660 μL of a 2.5 M solution in hexanes, 1.65 mmol, 1.65 equiv). The mixtures were heated to reflux, and stirred for 1 h, after which they were allowed to cool to room temperature. To the dark red mixtures were added various aldehydes (1.0 mmol) in THF (2 mL). The mixtures were heated to reflux, and stirred for 12 h, followed by allowing them to cool to room temperature. To the cooled mixtures was added saturated NH_4Cl (5 mL), and the mixtures were stirred for 30 min, followed by transferring the biphasic mixtures to a separatory funnel with diethyl ether (10 mL). The layers were separated, and the aqueous layer was extracted with ether (15 mL). The combined organic layers were washed with saturated NH_4Cl (10 mL), water (10 mL) and brine (10 mL). They were then dried over sodium sulfate, filtered, concentrated in vacuo, and the products purified by silica gel chromatography by eluting with 2% acetone in hexanes to give **41$_{Ar}$** along with the corresponding (*Z*)-**41$_{Ar}$** isomers. ^{1}H NMR analysis of the resulting mixtures allowed for the unambiguous determination of which allylic protons correspond to the **41$_{Ar}$** products produced in the preparation of the Hammett plot described above.

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CHAPTER 4

DEVELOPMENT AND EVALUATION OF ENANTIOSELECTIVE PD-CATALYZED HECK REACTIONS OF ACYCLIC SUBSTRATES

Introduction

Synthetic chemists have a vested interest in preparing optically active compounds, because biological systems typically respond uniquely to different enantiomers of the same molecule.[1] Therefore, in any synthesis intended to prepare a molecule fated to be submitted to biological activity assays, the synthesized target molecule should be enantiopure. Ideally, a substoichiometric amount of precious enantioenriched material may be used to impart optical activity upon a greater molar amount of prochiral substrate; in other words the small chiral molecule should ideally be used in a catalytic quantity. The catalytic enantioselective arylation and vinylation of alkene substrates using palladium catalysis, or the asymmetric Heck reaction,[2-4] is an example of such an efficient use of optically active material, in this case as the chiral ligand on a catalytic amount of palladium.

In 1989, when the seminal reports of the asymmetric Heck reaction were published,[5,6] most chiral catalysts employed in synthesis were those capable of oxidation[7] or reduction[8] reactions, and not those which install new carbon-carbon bonds. Therefore,

there has been great interest in the further development of asymmetric Heck reactions, and they have since been used successfully in the syntheses of a variety of natural products.[2,4] Most frequently, these reactions occur intramolecularly to give optically active intermediates that are then carried forward, ultimately to the target molecule (Figure 4.1 a). Intermolecular Heck variants capable of setting stereocenters in prochiral cyclic alkene substrates are known (Figure 4.1 b),[2] but there has been less progress made in the development of asymmetric intermolecular Heck reactions using acyclic substrates (Figure 4.1 c).[4,9] The mechanistic basis of this limitation is related to poor observed regioselectivity when using internal alkenes,[10-14] and to the unpredictable nature of β-hydride elimination (see Chapters 2 and 3). This leads to mixtures of products arising from non-selective insertion, isolated in racemic form due to racemization via β-hydride elimination. In contrast, upon facially selective insertion into a disubstituted cyclic alkene substrate, the newly formed stereocenter in intermediate **A** lacks a β-hydrogen in a *syn* relationship to palladium (Figure 4.2 a). In order to undergo β-hydride elimination, the metal center must instead engage a hydrogen atom residing on a carbon distal to the new stereocenter, resulting in an enantioenriched product bearing an olefin in a different position than the olefin present in the starting material. β-Hydride elimination thus occurs in a more predictable fashion, allowing the chemist to use this methodology to form new carbon-carbon bonds enantioselectively.

In contrast, when acyclic alkene substrates are used, bond rotation may occur to bring the hydrogen atom at the newly formed stereocenter in intermediate **B** into a configuration *syn* to palladium, and following β-hydride elimination, the intended stereocenter becomes an sp^2-hybridized carbon (Figure 4.2 b). The organometallic

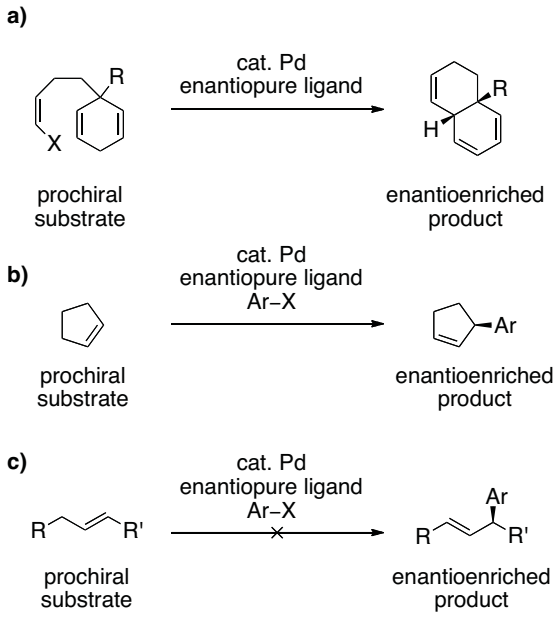


Figure 4.1. Generalized depictions of **a)** successful intramolecular asymmetric Heck reactions, **b)** successful intermolecular asymmetric Heck reactions using cyclic substrates, and **c)** unsuccessful intermolecular asymmetric Heck reactions using acyclic substrates.

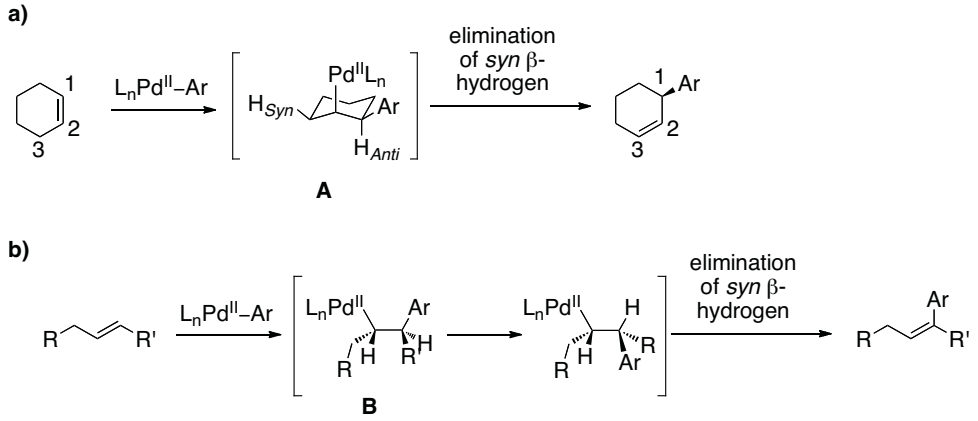


Figure 4.2. Mechanistic rationale for why **a)** cyclic alkene substrates can be used successfully in asymmetric Heck reactions, and **b)** acyclic alkenes cannot.

community's tenuous understanding of the factors that dictate selectivity in β-hydride elimination has, thus far, prevented a robust method for the asymmetric Heck reaction of acyclic alkene substrates. Based on the mechanistic understanding gained in Chapters 1-3, it was hypothesized that this obstacle could be overcome by employing a transition-metal catalyst capable of distinguishing between electronically inequivalent β-hydrogens in distinctive steric environments. The mechanistically guided development of an asymmetric Heck reaction is the subject of this chapter.

Background

Precedent for asymmetric Heck reactions: intramolecular variants

In 1989, the laboratories of Shibasaki[6] and Overman[5] independently reported the first catalytic asymmetric Heck reactions employing chiral bidentate phosphine ligands on palladium to induce enantioselective cyclizations (Figure 4.3). There are several similarities between the two reactions: both employ $Pd(OAc)_2$ as precatalysts which are reduced in situ to Pd^0, both use bidentate phosphine ligands, both use polar, aprotic solvents, and both reactions deliver products in optical purity that would be considered inadequate by modern standards. Shibasaki and coworkers used BINAP as the ligand to effect enantioselective construction of a *cis*-decalin structure, where the reactive site becomes a tertiary stereocenter (Figure 4.3 a). Importantly (vide infra) the reaction requires added silver salt to achieve efficient catalysis and stereoselectivity.[6] Overman and coworkers used DIOP, also a bidentate phosphine, as the ligand in a reaction in which two Heck cyclizations occur, the first of which constructs an all carbon quaternary

center (Figure 4.3 b).[5] The enantioselective construction of such centers remains a significant challenge in organic chemistry today.[15-18]

A key difference, with important mechanistic implications, between the two reactions is the fact that a vinyl iodide is used as the organic oxidant in Shibasaki's method, while a vinyl triflate is used by Overman and coworkers. The presence of iodide anion in the reaction mixture results in a mechanism where the metal center must dissociate from one of the two phosphines on the bidentate ligand in order to facilitate migratory insertion (Figure 4.4 a, neutral pathway).[4,19] In the absence of silver salts, this results in a reaction giving poor yield and poor regio- and enantio-selectivity, since the phosphine provides the chiral information relayed to the substrate. As Shibasaki reports, the results of his cyclization improve greatly with added silver salts, presumably because the silver cation removes the halide from solution.[6] This results in the mechanism depicted in Figure 4.4 b, referred to as a "cationic pathway,"[4] where both arms of the phosphine ligand are coordinated to palladium during the enantiodetermining migratory insertion step. After cyclization, a tetracoordinate palladium species is restored via coordination of a solvent molecule, or a different labile ligand. In contrast, Overman and coworkers use a substrate devoid of halides; instead oxidative addition results in the liberation of a weakly-coordinating triflate anion (Figure 4.4 c).[5] This is also a cationic pathway, because the triflate anion coordinates only weakly to palladium. Since there are no halide ions in solution, silver salts are not required as additives in order to achieve the results reported.

The implications of these mechanistic distinctions, namely that realizing high enantioselectivies in bidentate-ligated Pd-catalyzed Heck cyclizations requires a reaction

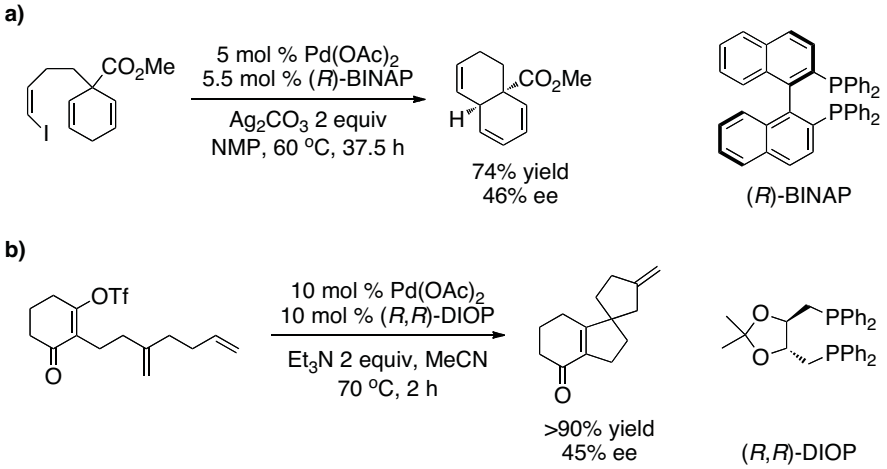


Figure 4.3. The first examples of asymmetric Heck cyclizations as reported by **a)** Shibasaki, and **b)** Overman.

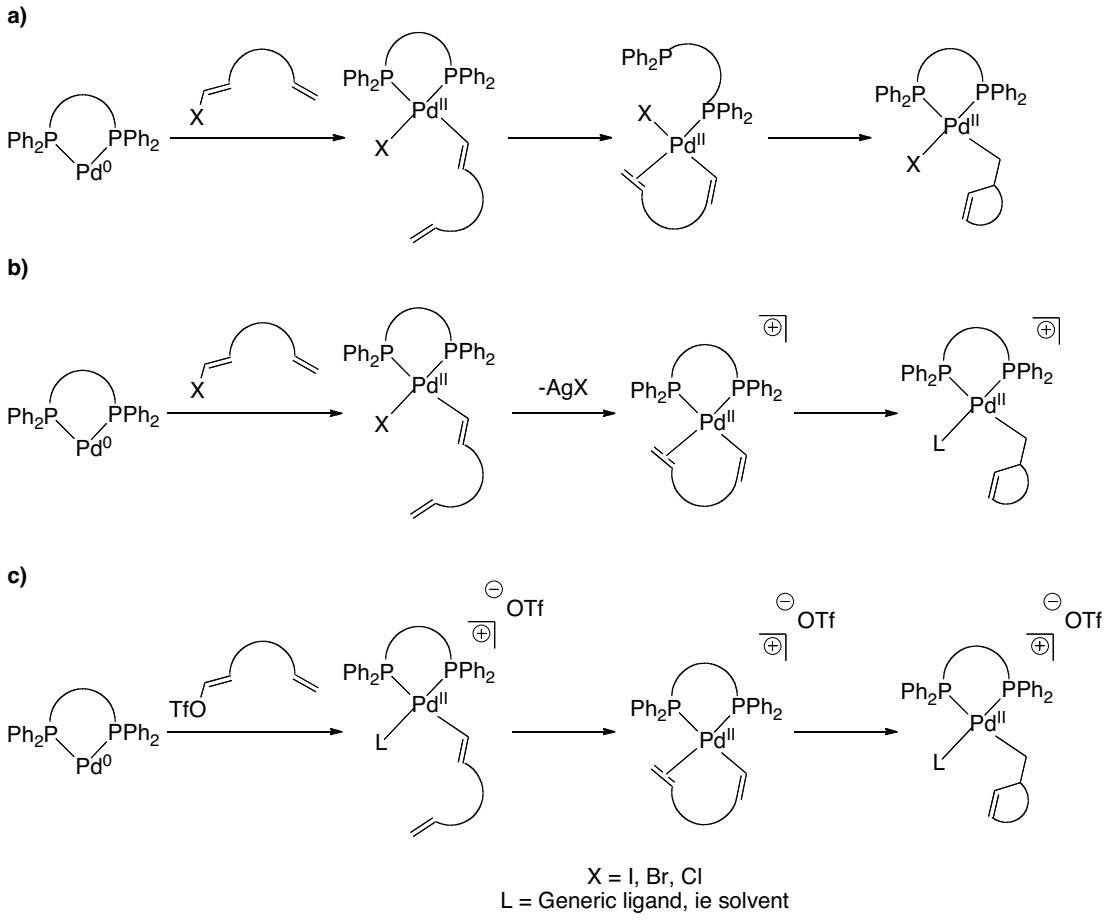


Figure 4.4. Pathways for asymmetric Heck cyclizations. **a)** Neutral pathway in the absence of silver salts. **b)** Cationic pathway by virtue of halide-scavenging silver additives. **c)** Cationic pathway by virtue of the weakly-coordinating triflate anion.

proceeding via a cationic pathway, were noted by the larger organometallic community. As such, much of the subsequent focus in developing more selective variants was on optimizing conditions using either organotriflates,[20,21] or organohalides in conjunction with various silver salts.[22-25] More obviously, the identity of the ligand used is important,[26-28] and many bidentate phosphine derivatives have shown promise in imparting high levels of enantioselectivity. The identity of the catalyst[26,29-31] and base[6]used in these transformations also has an influence on yield and enantioselectivity. More subtly, solvent selection is crucial,[32,33] since in cationic pathways a solvent molecule is proposed to be coordinated at various stages as the catalytic cycle progresses. The variation of these parameters is exemplified in the application of various conditions to asymmetric Heck cyclizations in the context of total synthesis.

Shibasaki and coworker's expended great effort to optimize an asymmetric Heck cyclization upon a vinyltriflate substate, which delivered an enantioenriched intermediate en route to the first asymmetric synthesis of (+)-vernolepin (Figure 4.5).[33] As is evident from the conditions, the addition of silver salts is not required, because an organotriflate is used as the oxidant, resulting in a cationic pathway without the need for these additives. To obtain the high enantioselectivity reported required extensive examination of the roles of base, solvent, and additives, with the most interesting observations relating to the choice of solvent. Typically, these reactions are performed in polar, aprotic solvents such as dimethylacetamide (DMA), or 1-methyl-2-pyrrolidinone (NMP), but the use of 1,2-dichloroethane (DCE) resulted in substantially higher optical purity in this case. Unfortunately, the use of this solvent also greatly diminishes the rate of the reaction, but the addition of KOAc resolved this issue to some degree. After the effort to

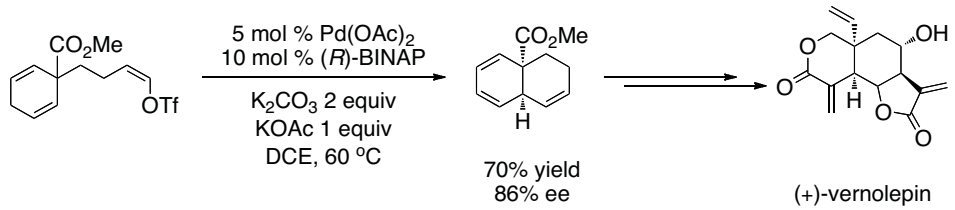


Figure 4.5. Shibasaki's use of an asymmetric Heck cyclization as the key step in a total synthesis of (+)-vernolepin.

optimize this transformation, the product was carried forward in the synthesis of the terpenoid natural product (+)-vernolepin, as described by Danishefsky.[34]

Shibasaki and coworkers completed the enantioselective syntheses of (−)-oppositol and (−)-prepinnaterpene also via the protocol utilizing a vinyl halide as oxidant in combination with a silver salt (Figure 4.6).[35] In this case, Ag_3PO_4 proved to be the best silver additive, and the group reported improved enantioselectivity using a pre-ligated catalyst, as compared to the addition of "naked" $PdCl_2$ along with the phosphine ligand. Again, BINAP was used as the source of chiral information, but in this case, the polar aprotic solvent NMP was optimal, which is typical of these transformations as discussed above. This example demonstrates that five-membered rings, in this case leading to hyndridane natural products, may also be formed enantioselectively using Heck cyclizations.

Although there are many examples of this reaction being used to construct rings enantioselectively in the pursuit of natural product syntheses,[4] one final example demonstrating the importance of the selection of experimental conditions should be mentioned. In this case, the Overman group targeted the alkaloid (−)-physostigmine,[36,37] and this example is interesting for several reasons. The first is that it requires the construction of an all-carbon quaternary center, and the Heck cyclization accomplishes

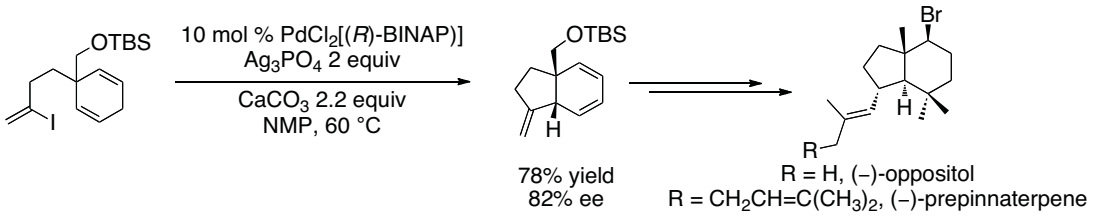


Figure 4.6. Shibasaki's syntheses of hyndridane natural products using asymmetric Heck cyclizations as the key step.

this exceptionally well under the optimized conditions, giving the cyclized product in 95% enantiomeric excess (ee) (Figure 4.7). The second point of interest concerns the conditions used: during optimization of the cyclization reaction shown in Figure 4.7, it was found that the use of the common silver additive, Ag_3PO_4, resulted in the formation of the *S* enantiomer (38% ee) of the product, while 1,2,2,6,6-pentamethylpiperidine (PMP) as additive predominantly gave the *R* enantiomer (45% ee). It is not obvious why this is the case, and the authors do not speculate. This additive is not an apparent halide scavenger, which makes the success of this transformation remarkable, given the use of an aryl iodide. The researchers report that the selection of olefin starting material isomers was crucial to observing high enantioselectivity; submission of the *E* alkene resulted in the low enantiomeric excess reported above, while submission of the *Z* isomer gave higher enantiomeric excesses using either Ag_3PO_4 or PMP. Interestingly, using the *Z* alkene isomer, employment of either additive led to the formation of the *R* enantiomer. This example, in combination with those outlined above, demonstrates the importance of experimentation in optimizing these transformations; it is not necessarily possible to predict optimal conditions a priori. Ultimately, the optimized cyclization, which also used a polar, aprotic solvent, proved to be the key reaction in a successful synthesis of the natural product.[36,37]

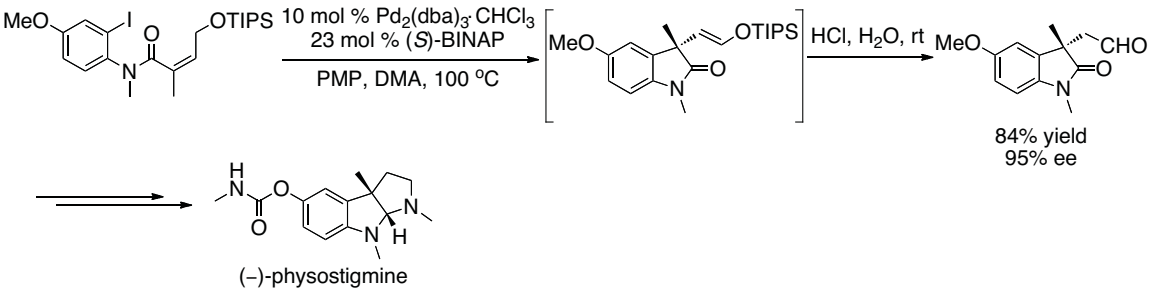
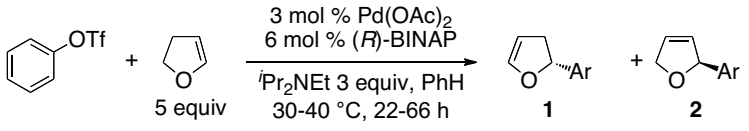


Figure 4.7. Construction of an all-carbon quaternary center in high enantiomeric excess using a Heck cyclization in Overman's synthesis of (–)-physostigmine.

Precedent for asymmetric Heck reactions: intermolecular variants using cyclic alkenes

The second historically successful class of asymmetric Heck transformations is intermolecular reactions between an aryl- or vinyl-nucleophile and a cyclic olefin substrate.[2,3] As discussed above, these reactions are capable of delivering product in high ee because the hydrogen atom at the newly formed stereocenter is inaccessible to palladium (Figure 4.2 a). The seminal report of an asymmetric intermolecular Heck reaction detailed the coupling of 2,3-dihydrofuran with aryl triflates in the presence of $Pd(OAc)_2$, with (*R*)-BINAP providing the chiral information (Figure 4.8).[38] A variety of different arenes could be installed, several of which are shown below, and in all cases a mixture of products, **1** and **2**, was obtained, each exhibiting optical activity. Interestingly, these products are delivered in opposite configuration, which was explained by invoking a kinetic resolution. Migratory insertion is proposed to occur on each face of the olefin, giving rise to diastereotopic Pd-alkyl complexes (**C** and **D**). β-Hydride elimination occurs from both complexes, but only the Pd-hydride complex leading to **1** (**E**) undergoes reinsertion in the opposite orientation. Finally β-hydride elimination occurs to deliver the



Ar	**1**/**2**	**1** ee	**2** ee
Ph	89/11	93	63
p-Cl	83/17	91	47
p-C(O)Me	80/20	93	53
p-OMe	72/28	73	66

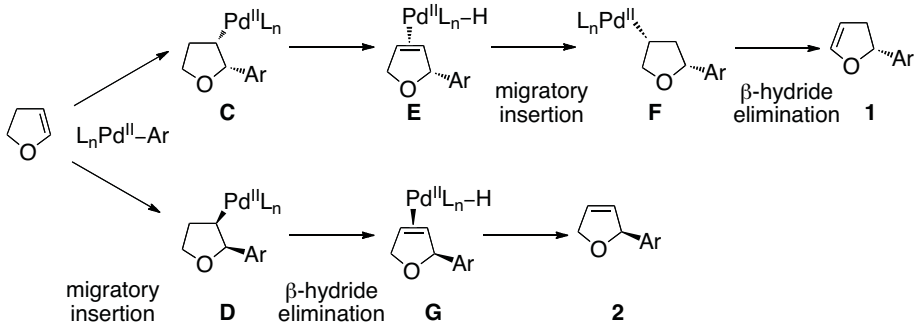


Figure 4.8. First asymmetric intramolecular Heck reaction, reported by Hayashi and coworkers, and explanation for product distribution.

reported a similar transformation of 2-pyrrolines.[39] It is important to note that the major product **1**. The minor product arises from β-hydride elimination, and dissociation of the observed product from **G** rather than reinsertion. Soon after, the same group substrate is an electronically biased olefin, which is likely responsible for the highly regioselective insertion.

Since this initial report, many different ligands have been used in rather similar transformations.[40-45] In the context of this discussion, however, more interesting and pertinent precedent is that detailing the extension of this type of chemistry to new substrates, since Heck reactions have historically been limited to particular substrate classes (see Chapters 2 and 3, and the background information above). Some of the reactions used to synthesize these alternative product types employ ligands other than

BINAP, which allows a discussion of ligand classes concurrently with that of the variety of products delivered.

Guiry and coworkers avoided the **1**-like products by utilizing substrates wherein that position is incapable of undergoing β-hydride elimination, and were thus able to extend this method to the synthesis of several new products (Figure 4.9).[46-48] Under optimal conditions, which call for the use of phosphinooxazoline ligand **3**, the products are obtained in good yield and excellent enantiomeric excess. The vinyl groups added using this methodology are arguably more synthetically versatile than their aromatic counterparts. However, these reactions take two weeks to achieve completion, diminishing the synthetic appeal. Hayashi reported superior results to those described by Guiry in the early 1990s (Figure 4.10).[49] Under these conditions, which employ a catalyst preligated to the reliable BINAP, a greater diversity of products are synthesized, in higher yields and enantioselectivities.

Heterocyclic alkenes bearing nitrogen atoms may also be cross-coupled in an enantioselective fashion as demonstrated by Hallberg and coworkers.[50] (*R*)-BINAP is employed as the chiral ligand, and the reaction is complete in a more timely fashion, although in both low yield and enantioselectivity (Figure 4.11). Hayashi obtained higher yields and enantioselectivities, with a greater demonstrated substrate scope, using similar conditions in benzene (Figure 4.12).[39] However, under Hayashi's conditions, a minor, but significant product arising from isomerization was also obtained (yields and enantioselectivities of the minor product are not shown).

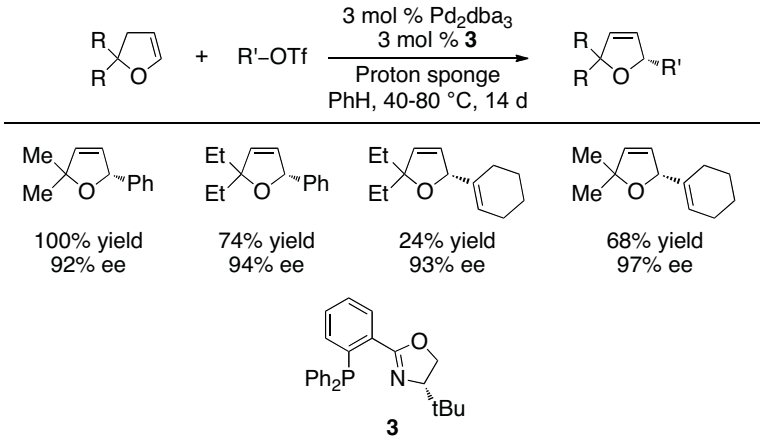


Figure 4.9. Guiry and coworker's extension of the scope of the intermolecular asymmetric Heck reaction.

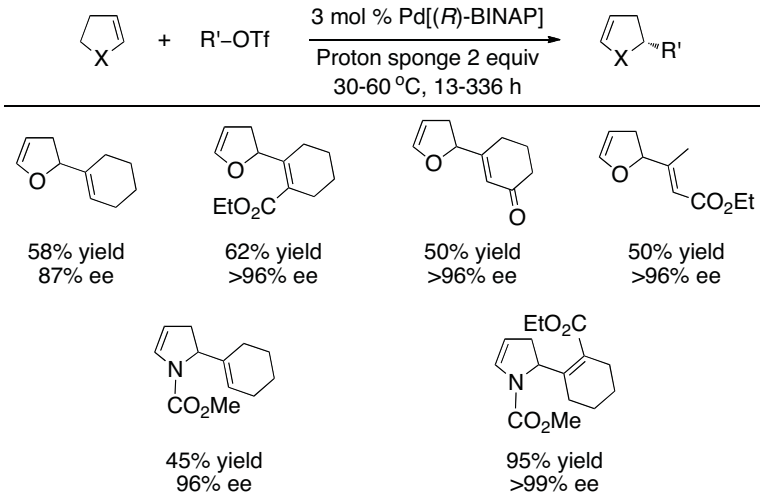


Figure 4.10. Hayashi's cross-coupling of heterocyclic alkenes and vinyl triflates.

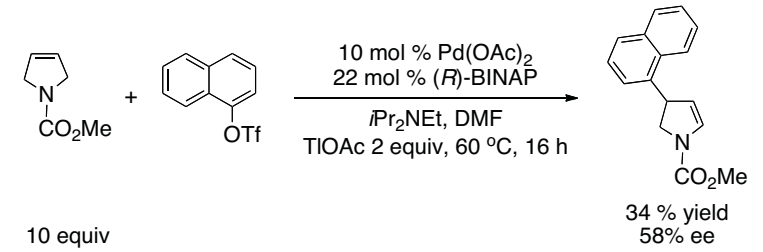


Figure 4.11. Hallberg's use of nitrogen-containing heterocycles in the intermolecular asymmetric Heck reaction.

More recently, Stoltz and coworkers reported an oxidative Heck-like reaction utilizing aryl boronic acids to add, in an enantioselective fashion, arenes to cyclic α,β-unsaturated ketones (Figure 4.13).[9] In this case, all carbon quaternary centers are set using chiral information relayed by the bidentate amine ligand Pyr*t*BOx, and thisrepresents the use of a substrate class distinct from those discussed above. It is a Heck-like reaction, because the carbon-carbon bond is formed via Heck insertion, but β-hydride elimination does not occur, because there are no β-hydrides. The class of ligands used is particularly attractive (vide infra) as they can be rapidly synthesized in a modular fashion using inexpensive picolinic acids and amino alcohols. This chemistry has added appeal arising from the use of arylboronic acids, many of which are commercially available. However, the method is limited to cyclic substrates, as the catalyst has not yet proven capable of selective β-hydride elimination.

Precedent for asymmetric Heck reactions: intermolecular variants

using acyclic alkenes

The intramolecular asymmetric Heck reaction using acyclic substrates has received little attention, due to poorly regioselective migratory insertion, and to unpredictable β-hydride elimination as discussed above.[4] The first example leading to any enantioenrichment of product utilized a bidentate phosphorus/amine ligand derived from glucosamine, **4**, to impart enantioselectivity in the addition of a phenyl group to crotyl alcohol (Figure 4.14).[51] This was an exciting result, as it was the first indication that this type of transformation was possible, but the optimal conditions gave the product in only 17% ee. It should be noted that the product isolated in this reaction results from β-

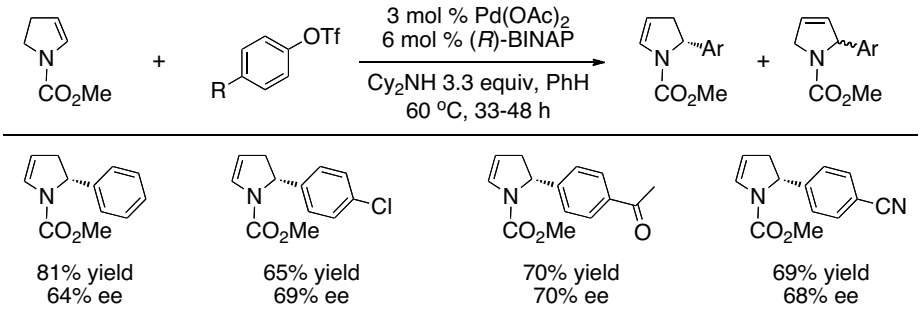


Figure 4.12. Hayashi's results using *N*-substituted-2-pyrrolines.

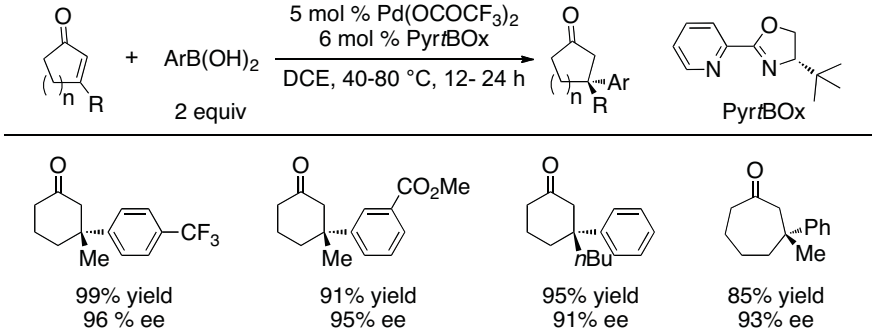


Figure 4.13. Stoltz and coworker's enantioselective oxidative Heck reaction of cyclic enones.

hydride elimination of the carbinol hydrogen, which results in enol, and this ultimately tautomerizes to the aldehyde observed. This remains the only example of an asymmetric Heck reaction using an acyclic olefin substrate catalyzed by Pd^0.

Several years later, Jung and coworkers reported significantly better results using the Pyr*t*BOx ligand, and a different substrate class under oxidative conditions.[52] The reaction improved upon the yields and enantioselectivities delivered by the Pd^0-catalyzed reaction described above, and is capable of cross-coupling acyclic alkene substrates with a variety of arenes (Figure 4.15). In this transformation trisubstituted alkenes are submitted to oxidative Heck catalysis with arylboronic acid derivatives. After the facially selective migratory insertion step, the catalyst preferentially engages a hydrogen

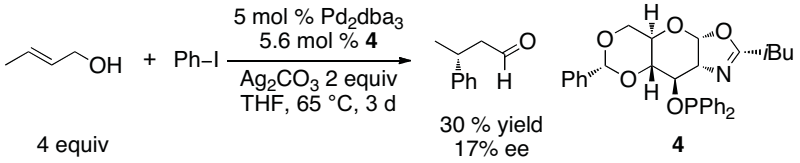
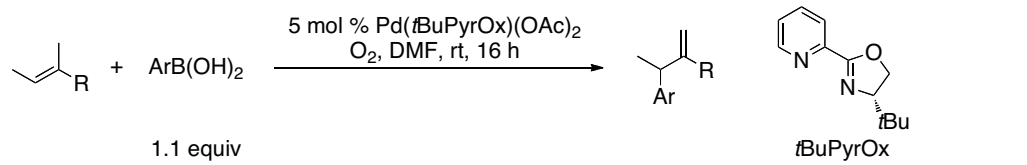


Figure 4.14. Uemura and coworker's discovery of the first asymmetric intermolecular Heck reaction of an acyclic substrate.



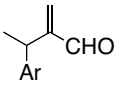
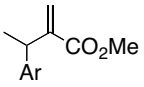
					
Ar = Ph	74% yield	75% ee	Ar = Ph	67% yield	69% ee
Ar = *p*-MeOPh	67% yield	73% ee	Ar = *p*-MeOPh	76% yield	75% ee
Ar = *p*-Me_2NPh	79% yield	75% ee	Ar = 6-MeO-2-Naphthyl	75% yield	62% ee

Figure 4.15. Jung and coworker's system, which exhibits greatly improved yield and enantioselectivity.

atom on an adjacent methyl group, rather than rehybridizing the newly formed stereocenter. While the initial publication reported greatly improved results, the enantiomeric excesses of these products left room for improvement.

In 2010 Jung and coworkers were able to improve on their initial report, extending the methodology to deliver a greater variety of products with higher levels of enantioselectivity.[53] Under these new conditions, a tridentate *N*-heterocyclic carbene-amidate-alkoxide ligand (**5**) was optimal, giving enantiomeric excesses over 90% for the first time (Figure 4.16). This reaction also utilized arylboronic acids under an O_2 atmosphere, and proceeds at room temperature in a timely fashion. Many of the products formed in Jung's 2007 report (not shown) were formed in higher optical yields, and the method was extended to products not reported in the initial publication. When work

began on the development of a transformation of this type in the Sigman laboratory, Jung's work indisputably represented the state of the art in this type of transformation using acyclic substrates.

Heck reactions delivering optically active acyclic products:

chirality transfer

A different mechanistic strategy to address the problems associated with the use of acyclic alkene substrates has been reported, with limited success. In this case, optically active allylic alcohols were submitted to "ligandless" Pd^0-catalyzed Heck reactions, where the stereochemical integrity of the carbinol stereocenter was transferred, to a modest degree, to the newly formed stereocenter β to the ketone in the product.

Georgoulis was the first to report success using this strategy (Figure 4.17), but was able to transfer only 1.7% and 8.5% of the starting material's optical activity using (*E*)- and (*Z*)-(*R*)-pent-3-en-2-ol, where the products were obtained with opposite configurations.[54] Clearly, this is not a mature method for the synthesis of highly enantioenriched β-aryl ketones using the Heck reaction. Henry conducted a similar experiment ten years later under oxidative Heck conditions (Figure 4.18).[55] While the transfer of stereochemical integrity was much improved (potentially due to the fact that these experiments were conducted at room temperature), this remains an inefficient method for the preparation of enantiomerically enriched β-aryl ketones. The authors of each report do not offer an explanation of the mechanistic origin of the inefficiency observed in the chirality transfer by invoking a racemization via β-hydride elimination

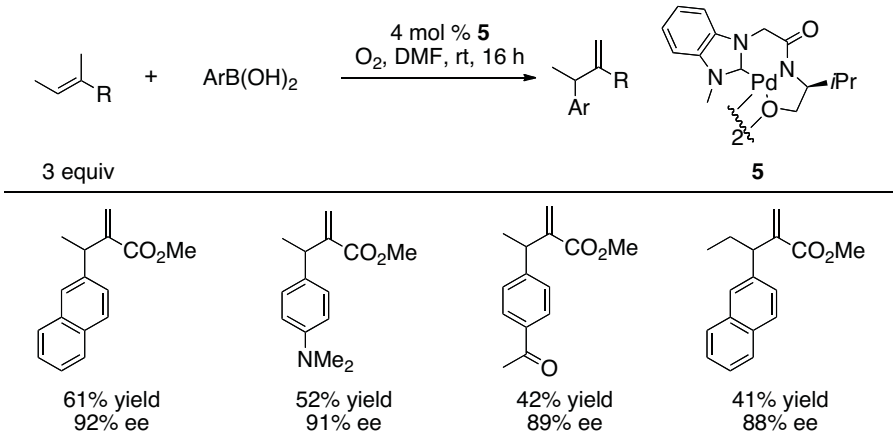


Figure 4.16. Jung's 2010 report improving upon previous results, and using a different ligand.

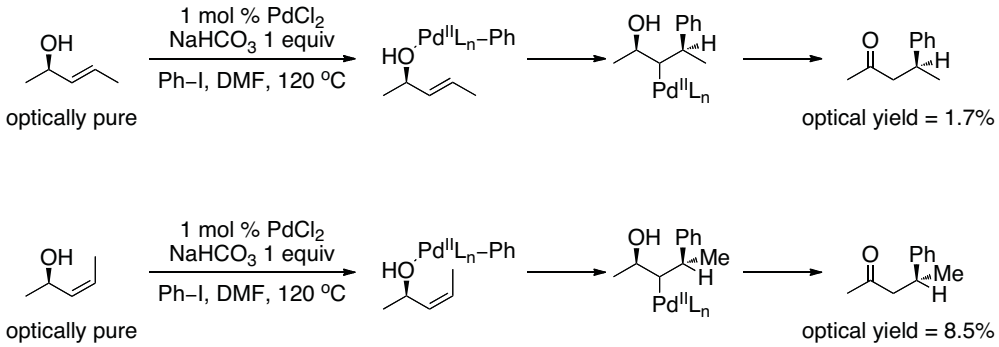


Figure 4.17. Georgoulis's chirality transfer experiments using the Pd^0-catalyzed Heck reaction.

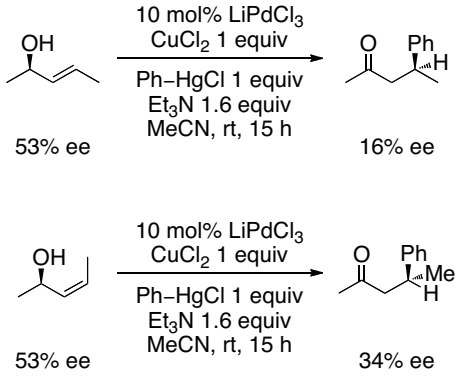


Figure 4.18. Henry's chirality transfer experiments using the oxidative Heck reaction.

pathway, but it is certainly possible that this leads to some of the loss of stereochemical integrity observed in the products.

Enantioselective conjugate addition chemistry

The optically active β-aryl ketone products delivered using the chirality transfer strategy may also be synthesized using alternative methods, with higherenantioselectivity than was observed by Georgoulis or Henry. It is important to discuss these methods, because it was envisioned that these products could be obtained using an improved asymmetric Heck reaction (vide infra). Nucleophiles may be added to electron-deficient olefins enantioselectively using various transition metals, with much of the existing study focusing on the Rh-catalyzed Michael addition of arylboronic acids to enones.[56] The seminal report,[57] where β-aryl ketone products were obtained in high enantioselectivity from enones (Figure 4.19), was published in 1998 by Hayashi, who also reported many of the asymmetric Heck reactions described above. Similar to Hayashi's work in palladium catalysis, the ligand used in this transformation is BINAP, but following this report many other ligand classes were found to induce similarly enantioselective 1,4-additions.[58-65] For reasons that are unclear, the abundance of subsequent papers describing this reaction report the use of essentially the same substrates, with few examples of compatible substrates bearing diverse functional groups, or even examples reporting the use of more diverse hydrocarbon alkenes. According to the philosophy of the Sigman group, it is important to demonstrate that diverse product structures are accessible via new methodology, which provides significant opportunity for improvement upon this conjugate addition method.

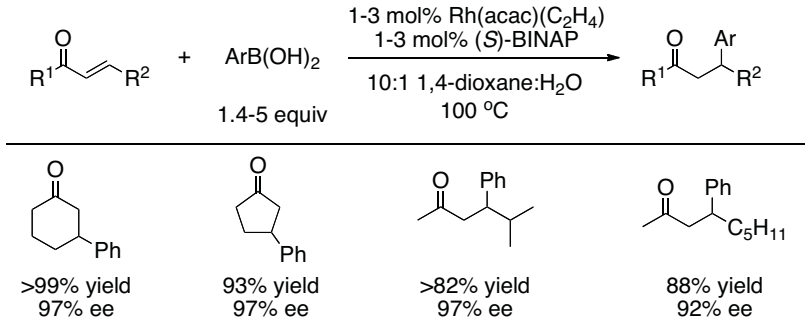


Figure 4.19. Hayashi's seminal report describing the Rh-catalyzed enantioselective 1,4-addition of arylboronic acids to enones.

There are several exceptions to this homogeneity in demonstrably accessible products using chiral rhodium catalysts to induce asymmetric Michael additions. Soon after Hayashi's seminal report using enones, the same group reported that α,β-unsaturated esters were compatible with the methodology, delivering β-aryl esters with high enantioselectivity (Figure 4.20).[66] This discovery has been confirmed by Miyaura and coworkers,[67] and extended to the use of α,β-unsaturated amides with similar results.[68,69] In addition to this modest variation in product classes accessible using Rh-catalyzed Michael additions, various nucleophiles have been added to these substrates, including those derived from vinylboronic acids.[57,70]

The mechanism of this transformation is distinct from that proposed for Heck reactions, which involves migratory insertion followed by β-hydride elimination. Instead,the mechanism begins with transmetalation of Rh^I with the arylboronic acid, followed by migratory insertion (Figure 4.21).[56] This results in a rhodium-enolate complex, **H**, which is hydrolyzed by the water in the solvent mixture, rather than undergoing β-hydride elimination. With this hydrolysis mechanism operative,

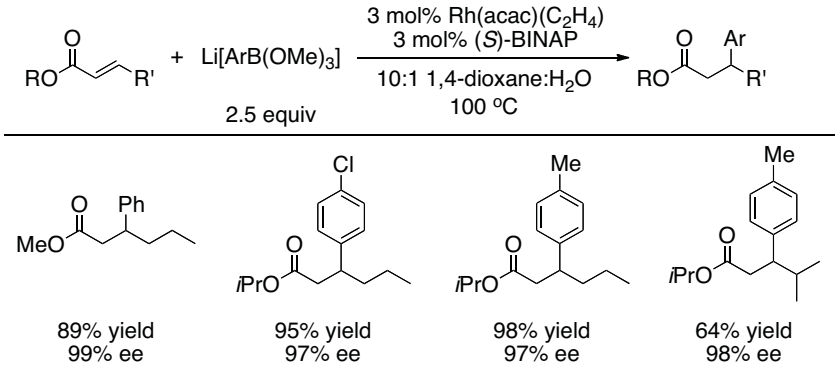


Figure 4.20. Hayashi's use of α,β-unsaturated esters in the asymmetric conjugate addition reaction.

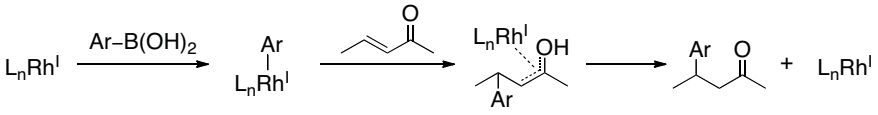


Figure 4.21. Mechanism of enantioselective Rh-catalyzed Michael additions.

racemization of the newly-formed stereocenter via β-hydride elimination (vide supra) is not a pathway by which product enantiomeric excesses suffer.

Mechanism-Based Strategy for the Development of an Asymmetric Heck Reaction

With the discovery that catalyst controlled β-hydride elimination was possible, based on the results and mechanistic experiments described in Chapters 2 and 3,[71,72] a robust solution to the intermolecular asymmetric Heck reaction using acyclic alkene substrates seemed within reach. The observation that carbinol and benzylic hydrogens (H_C and H_B) undergo competitive β-hydride elimination (Figure 4.22 a), resulting in approximately equal amounts of ketone and allylic alcohol products, led to the hypothesis that these types of hydrogens were electronically similar in terms of their hydridic nature.

It was hypothesized that, given these hydrides' competitive electronic nature, a catalyst with similar electronic properties could be induced to select for carbinol hydrides over benzylic hydrides based upon influence of an added variable. Specifically, the relative steric environments of these electronically competitive hydrides could provide a basis by which the catalyst could distinguish between them, if a 1,1-disubstituted alkene bearing an allylic alcohol was used as the substrate (Figure 4.22 b). Therefore, to successfully develop an asymmetric Heck reaction based on this strategy, it would be necessary to use a metal center that was highly electrophilic, by virtue of weakly-coordinating counterions, to allow for catalyst-controlled β-hydride elimination (see Chapters 2 and 3). The system would also have to employ a bulky ligand, which did not disrupt the electrophilicity of the metal center, to distinguish between electronically similar hydrides based on their relative steric environments. If the migratory insertion event could be rendered regioselective, based on the inductive effect provided by the hydroxyl group, and enantioselective, using a chiral ligand, the newly formed stereocenter could be prevented from racemizing via β-hydride elimination, due to the catalyst selecting for the carbinol hydrogen based on this combination of steric and electronic factors.

At the outset, the use of bidentate ligands was anticipated to lead to the successful development of such a transformation. These ligands were targeted partially due to their successful employment in intramolecular asymmetric Heck reactions,[4] and in intermolecular variants using cyclic alkene substrates.[9] The use of these ligands would also render the configuration of the allylic alcohol starting material irrelevant, because the bidentate-ligated catalyst's remaining coordination sites would be occupied by the arene and the olefin in the enantiodetermining insertion step. This would allow for the

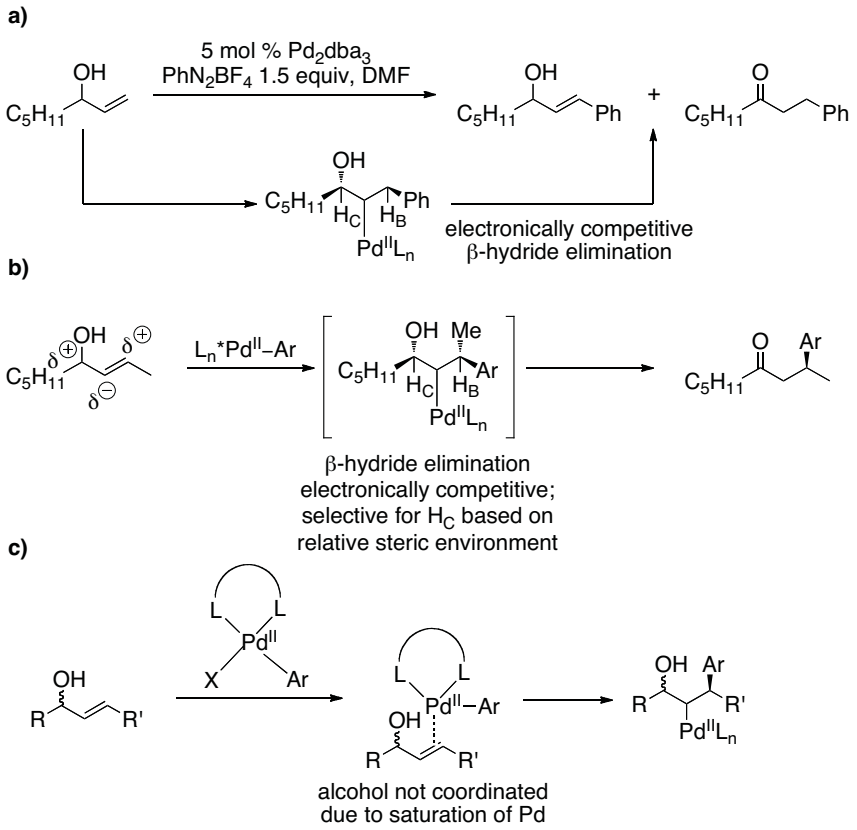


Figure 4.22. a) Carbinol and benzylic hydrogens undergo β-hydride elimination competitively based on their electronic nature. **b)** Hypothesized enantioselective Heck reaction using acyclic allylic alcohols and mechanistic rationale. **c)** The proposed use of bidentate ligands would allow for the use of racemic allylic alcohols as substrates.

use of racemic allylic alcohols as starting materials in the preparation of optically active β-functionalized carbonyl products, providing an obvious advantage over the chirality transfer strategy (Figure 4.22 c).

If the proposed reaction were successfully developed, it could also be possible to extend this strategy to deliver products inaccessible to current methods known to organometallic chemists (vida infra). As discussed above, the initially targeted β-aryl carbonyl products may be obtained by enantioselective 1,4-addition reactions to α,β-unsaturated carbonyls, a known class of reactions.[56,57,73-80] From a synthetic standpoint, however, the proposed methodology would serve both to form the new carbon-carbon

bond enantioselectively, and simultaneously oxidize the alcohol to give the carbonyl moiety. This concurrent functionalization of two groups, along with the mechanistic differences between this transformation and Michael addition chemistry, provided additional incentive to pursue development of the proposed reaction.

Development of an enantioselective Heck reaction of allylic alcohols

Initial attempts to develop an enantioselective Heck reaction of allylic alchols focused on the use of aryl iodides and chiral bidentate phosphine ligands, anticipating that this would allow for the use of mild temperatures. Not surprisingly, these attempts failed, resulting in only small amounts of the desired product, **6**, when using some of the ligands surveyed, but in racemic form (Figure 4.23).

After confirming that the presence of iodide anion in the reaction mixture was incompatible with an enantioselective Heck reaction,[4] chirality transfer experiments were conducted with greater relative success. In this case, enantioenriched allylic alchols, **7**, were submitted to the previously optimized conditions for the Pd^0-catalyzed Heck reaction using aryldiazonium salts, leading to partial transfer of optical activity in the ketone product, **8** (Figure 4.24). While this represented a significantly better result, in terms of efficiency of chirality transfer, than had been reported in the literature,[54,55] it was deemed both insufficient to warrant further pursuit, and less attractive than the initially proposed reaction. For this reason, more consideration was given to the choice of arene source, and of chiral ligand.

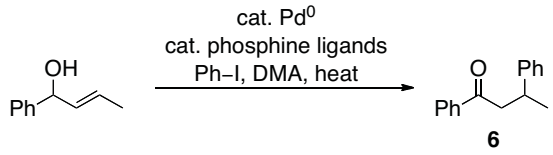


Figure 4.23. Failed attempts to develop an enantioselective Heck reaction using iodobenzene and chiral bidentate phosphine ligands.

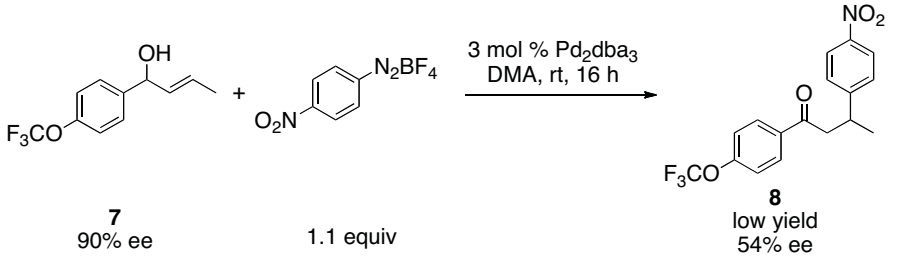


Figure 4.24. Limited success in chirality transfer experiments.

The virtues of aryl diazonium salts, namely their propensity to undergo facile oxidative addition and the resulting weakly-coordinating counterion,[72,81,82] seemed ideally-suited to the development of an asymmetric Heck reaction. Similar to the reasons for choosing these reagents for evaluation in the development of the classical Heckreaction (see Chapter 3), it was thought that the low temperature required to arrive at a cationic Pd^{II}-aryl species via oxidative addition could facilitate an enantioselective transformation. However, these salts had never been used successfully in asymmetric catalysis, a fact that is stated explicitly in two reviews detailing the employment of these reagents.[83,84] After consideration, it seemed likely that this dearth of precedent may be a result of previous researchers' attempts to used aryl diazonium salts in conjunction with phosphine ligands. These nucleophilic additives would likely attack the electrophilic arenes, resulting in the consumption of both the ligand and some of the arene source.Modern asymmetric catalysis researchers have successfully used a greater variety

of chiral ligands to impart optical activity than were previously known, including many that do not contain phosphorous atoms, such as bidentate amine ligands.[9,85-90] Ligands of this type were envisioned to be potentially compatible with aryl diazonium salts as they should be less nucleophilic than phosphine ligands. Additionally, the Sigman group had previously realized success using these ligands in a variety of transformations,[91,92] including in asymmetric catalysis,[85,93,94] and an existing "ligand library" was available without the need for synthesis.

The quinoline oxazoline (QuinOx) and PyrOx ligands in particular seemed well suited for employment in the envisioned transformation. These ligands exhibit an "electronic asymmetry" by virtue of the relatively electron-deficient pyridine moiety as compared to the electron-rich oxazoline module (Figure 4.25).[90,95] The electronic disparity between the two nitrogen atoms, which are proposed to coordinate with palladium, has been implicated in the success of both a catalyst-controlled Wacker oxidation,[95] and an enantioselective aza-Wacker cyclization.[89] Studies in the Sigman laboratory suggest that the relatively electron-rich oxazoline moiety will preferentially coordinate *trans* to the more anionic reacting species (in this case an arene).[95] This leaves the electron-poor pyridine to coordinate *trans* to the less nucleophilic reactant (in this case the olefin) (Figure 4.25). Preferential coordination in this fashion should lead to a well-defined complex, envisioned to be important when using a C_1-symmetrical ligand, with the ligand's chiral center in close proximity to the reacting olefin. Additionally, as mentioned above, the synthesis of these ligands is relatively straightforward, and the modular building blocks are commercially available.

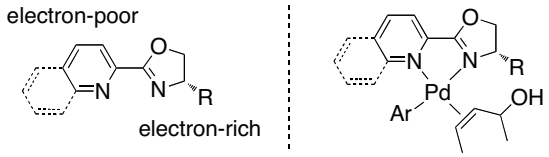


Figure 4.25. Quinox and PyrOx electronic asymmetry, and envisioned role of asymmetry in the proposed enantioselective Heck reaction.

A ligand used in the asymmetric dialkoxylation of styrenes,[85] named *i*PrQuinox, was tested for compatibility with aryldiazonium salts, and provided the first indication that asymmetric catalysis was indeed possible using these reagents (Figure 4.26 a). The low yield and enantioselectivity of this reaction aside, this demonstrated proof-of-concept, and future efforts were focused on optimization using this general class of ligands. Significant improvement over this result was observed when 4-CF_3Py*t*Box was used, resulting in an enantiomeric ratio (er) of 88:12, although in low yield of the same β-aryl ketone product. All experiments employing the benzaldehyde-derived substrate, **9**, had delivered complex mixtures of products in experiments utilizing aryldiazonium salts, with byproducts arising from acid-induced rearrangements of the starting material (Figure 4.26 b). Additionally, the products required purification to allow for the assay of enantiomeric excess, so a simpler substrate, **10**, was chosen. The starting material and product, **11**, could be assayed in crude form using gas chromatography. A similar er was observed using this substrate, and it was chosen for further optimization (Figure 4.26 c).

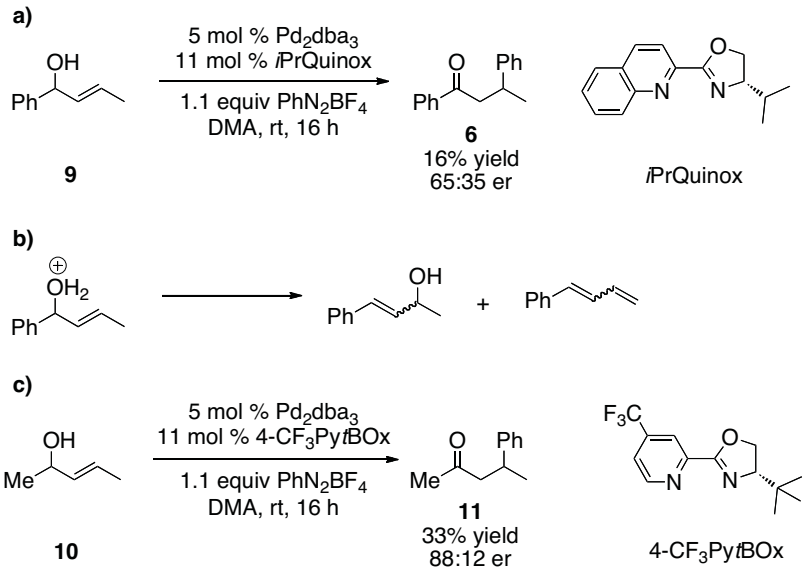


Figure 4.26. a) Initial enantioselective result using *i*PrQuinOx. **b)** Acid-mediated rearrangement to deliver byproducts of the reaction using benzaldehyde-derived substrate. **c)** Initial result using aliphatic substrate and CF_3Py*t*BOx.

Optimization of the Enantioselective Heck Reaction Using Allylic Alcohols

A fellow member of the Sigman group, Kaid Harper, conducted successful research developing techniques to predict reaction outcomes (in terms of enantioselectivity) using untested ligands based on a mathematical model of how similarligands perform experimentally.[93,96] One of the primary motivations for this research is to streamline the often-tedious process of reaction optimization, while also investigating the synergistic effects of seemingly unrelated factors, namely the steric and electronic properties of distinct ligand substituents (Figure 4.27 a). Harper has successfully used this technique both to identify an optimal ligand within a given class, and also to determine that a given ligand class will not give the desired results regardless of substituent combinations. This latter achievement, while not necessarily conducive to publishing optimized reactions, allows the chemist to abandon work attempting to

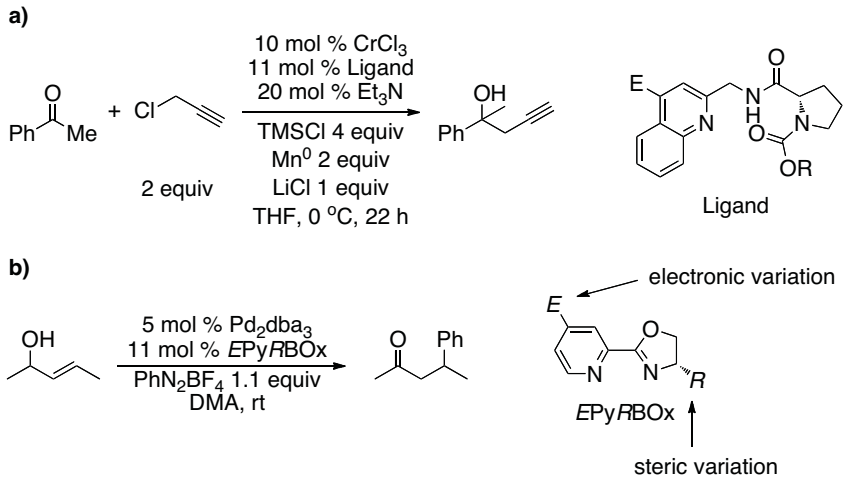


Figure 4.27. a) Harper's asymmetric ketone propargylation reaction, using a ligand identified by three-dimensional modeling. **b)** Model asymmetric Heck reaction and steric and electronic perturbations intended.

identify an optimal ligand variant early in reaction development. In a practical sense, this potentially saves a great deal of time and resources that would otherwise be invested in the synthesis of doomed variants of a given ligand class. At the time when optimization was required for the enantioselective Heck reaction, this method of optimization had only been applied to the development of enantioselective chromium-catalyzed carbonyl allylation and propargylation reactions. Given the obvious differences between Nozaki-Hiyama-Kishi chemistry and the desired palladium-catalyzed enantioselective Heck reaction, and the appealing prospect of avoiding tedious ligand optimization, this method was employed to identify an optimal ligand within the PyrOx class. Specifically, rapid Hiyama-Kishi chemistry and the desired palladium-catalyzed enantioselective Heck reaction, and the appealing prospect of avoiding tedious ligand optimization, this method identification of the ideal steric bulk of the oxazoline substituent in combination with the optimal electronic properties of the pyridine substituent was desired (Figure 4.27 b).

The method calls for an array of carefully chosen target ligands, where the steric bulk of the oxazoline substituent varies as widely as is synthetically feasible, while the data points are as evenly spaced as possible. The electronic parameter, as represented by the substituent on pyridine, should likewise vary widely with evenly spaced data points. The purpose of a large range of each parameter is to allow for accurate prediction within as large a space as possible, while the evenly spaced data points ensure that the model is not weighted to provide more data in one region than another. With this in mind, a nine-ligand library was identified as the target, and synthesized by previously reported methods commonly employed in the Sigman group (Figure 4.28).[85,86,91,92,95] It quickly became clear that many of the target ligands were unstable, and thus, were used as quickly as possible after synthesis, without full characterization. In particular, the ligands with electron-rich pyridine substituents, such as **12**-**14**, or those with small R groups, especially Me, decomposed rapidly, while electron-deficient variants were stable and much easier to work with. The ligand, **12**, bearing methyl groups on both the pyridine and the oxazoline was ultimately not synthetically accessible.

The use of these ligands in the asymmetric Heck reaction using the simple substrate **10** resulted in product formation in various yields and enantiomeric ratios (ers) (Table 4.1). Plotting the ers as a function of the Hammett electronic parameters of the pyridine substituent, and the steric parameters of the oxazoline substituent resulted in a mathematical model correlating predicted and experimental ers. The plot in Figure 4.29 demonstrates the high quality of the model generated, and allows the chemist to predict how perturbations in these parameters will affect the enantioselectivity of the reaction (Figure 4.29). Analysis of this data led to the conclusion that the steric bulk of the

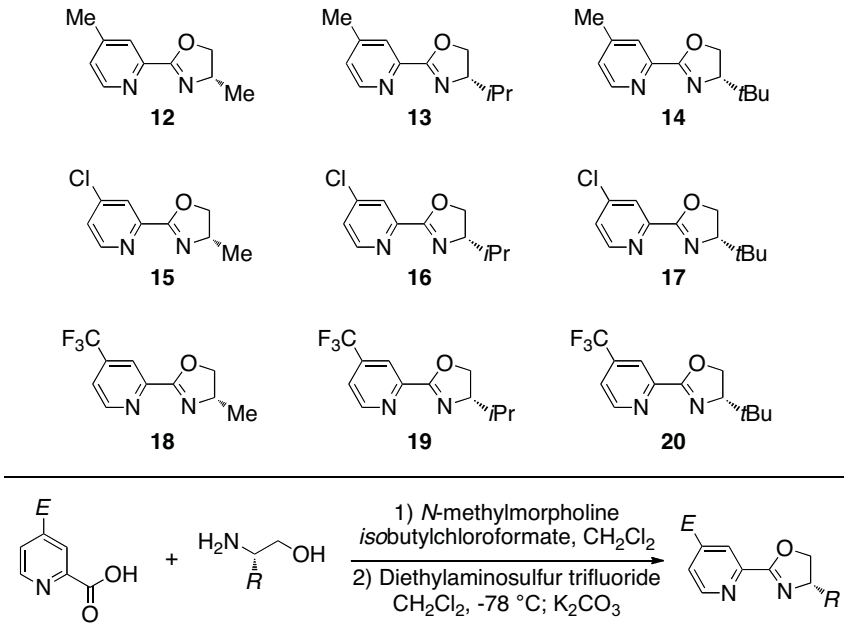
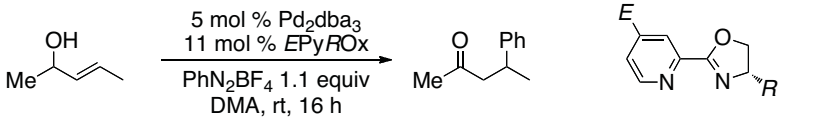


Figure 4.28. Nine-membered ligand library targeted, and synthetic route to ligands.

Table 4.1. Yield and enantiomeric ratio data for the asymmetric Heck reaction of substrate **10**, using the nine-membered PyrOx ligand library.



10 **11** *E*Py*R*Ox

Ligand	yield[a]	er[b]
E = Me, R = Me, **12**[c]	NA	NA
E = Me, R = *i*Pr, **13**	38.1	91.5:8.5
E = Me, R = *t*Bu, **14**	47.7	90.0:10
E = Cl, R = Me, **15**	27.3	64.0:36.0
E = Cl, R = *i*Pr, **16**	35.7	72.7:27.3
E = Cl, R = *t*Bu, **17**	58.7	90.9:8.1
E =CF_3, R = Me, **18**	25.5	63.5:35.5
E = CF_3, R = *i*Pr, **19**	43.8	70.2:29.8
E = CF_3, R = *t*Bu, **20**	57.4	91.5:8.5

[a]Yield was calculated by comparing product peak integration to integration of an internal standard using corrected GC analysis. [b]er was determined by comparing enantiomer product peak integrations using chiral GC analysis. [c]Ligand was synthetically inaccessible.

oxazoline substituent, not surprisingly, has a large influence on the enantioselectivity of the reaction. However, the electronic nature of the pyridine substituent also affected er to a lesser extent. It also led to the conclusion through extrapolation that a bulkier oxazoline substituent, such as an adamantyl group, would not lead to a significantly higher er, and so these ligands were not synthesized. The yields using ligands bearing electron-withdrawing pyridine substituents were generally higher than those bearing electron-donating groups, and these ligands were significantly more stable. Upon the basis of these considerations, the optimal ligand was that bearing a pyridine 4-CF_3 substituent, and a *tert*-butyl oxazoline substituent, **20**. However, the carboxylic acid required for the synthesis (Figure 4.28) of this ligand was quite expensive (~ $120/gram), and an analogue bearing the CF_3 group in the 5-position costs significantly less (~ $40/gram). The ligand, **21**, derived from this acid was anticipated to perform similarly, in terms of enantioselectivity, based upon the mathematical model. It was also anticipated to deliver similar yields to that of the 4-CF_3 variant, **20**, and based upon previous synthetic experience, was expected to be stable. Therefore, the ligand, **21**, bearing a CF_3 in the 5-position of the pyridine, and the oxazoline derived from *tert*-leucinol, was selected for further optimization.

Following the identification of the optimal ligand within the PyrOx ligand class, modest optimization, using decreased catalyst loading for economic reasons, was performed to maximize product yield and enantiomeric ratios (Table 4.2). For example, changing solvents from DMA to DMF resulted in a slight improvement in enantiomeric ratio (entry 1 vs 2), as did changing the aryl diazonium salt counterion from BF_4 to PF_6 (entry 2 vs 3). Increasing the loading of the arene source significantly improved the yield

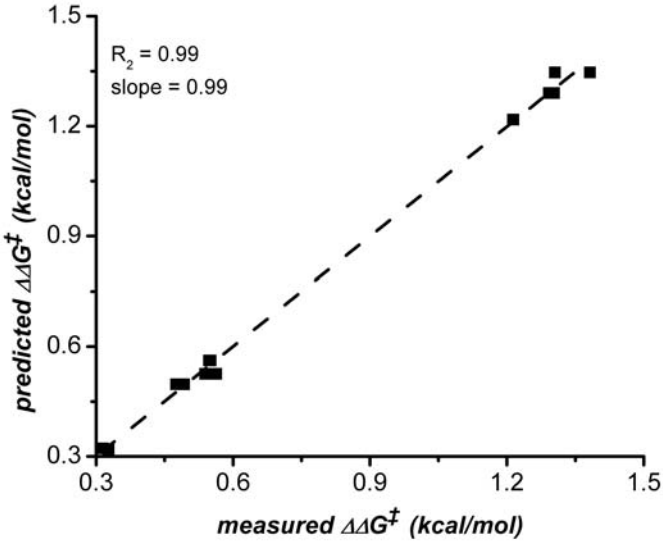
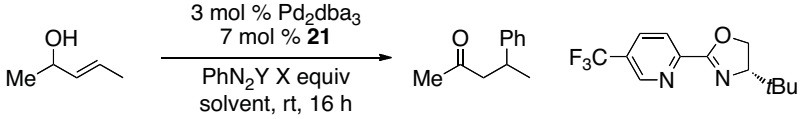


Figure 4.29. Mathematically predicted, vs experimental ers demonstrating the predictive ability of the model.

Table 4.2. Optimization of asymmetric Heck reaction using Ligand **21**.



10 **11** **21**

entry	X	Y	Solvent	%conversion[a]	%yield[a]	er[b]
1	1.1	BF_4	DMA	85.6	41.2	91.2:8.8
2	1.1	BF_4	DMF	100	58.7	92.7:7.3
3	1.1	PF_6	DMF	100	41.9	93.8:6.2
4	2.2	PF_6	DMF	100	70.5	93.7:6.3

[a]Yield was calculated by comparing product peak integration to integration of an internal standard using corrected GC analysis. [b]er was determined by comparing enantiomer product peak integrations using chiral GC analysis.

of the reaction, while resulting in a modest decrease in er (entry 4). Entry 4 represented the final optimized conditions, and these were used to evaluate substrate scope.

Evaluation of Substrate Scope

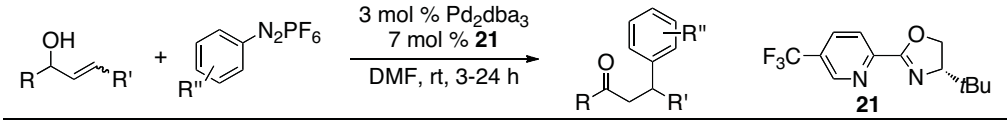
As mentioned in the background information section of this chapter, transition-metal-catalyzed Michael addition reactions have not been reported to exhibit high functional group tolerance, and it is important to demonstrate that newly-developed methodology is robust in this respect. Therefore, most of the substrate scope was performed using functionalized aryldiazonium salts, rather than installing unsubstituted phenyl groups. For example, submission of the simple substrate, **10**, used to optimize the reaction to coupling with an ester-substituted diazonium salt on 0.5 mmol scale gave 72% yield of **22** with 93:7 er (Table 4.3, entry 1). The use of a ketone-bearing diazonium salt resulted in similar yield of the corresponding product (**23**), while the submission of a substrate bearing a bulkier group on the saturated side of the ketone gave **24** with a higher enantiomeric ratio (entry 3). This substrate also performed well when coupled with an arene bearing a ketone substituent (delivering **25**). Interestingly, the submission of the same substrate, except with *Z*-alkene geometry, resulted in a slightly higher yield of **25**, but with the opposite configuration at the newly-formed stereocenter (entry 5). While this could provide additional synthetic appeal, since one can synthesize either enantiomer of a desired compound without having to make both ligand enantiomers, it also demands configurational purity of the starting alkene for successful asymmetric catalysis.

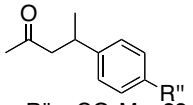
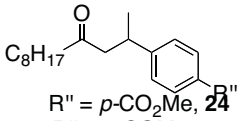
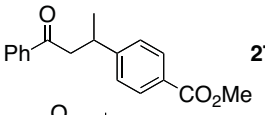
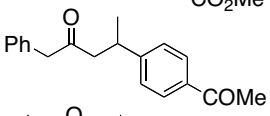
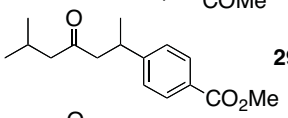
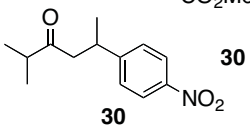
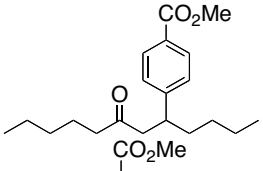
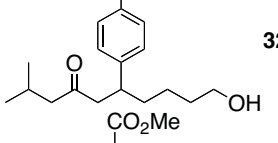
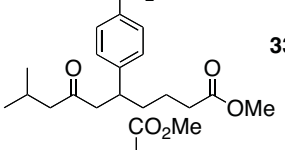
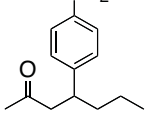
The installation of an iodide-bearing arene proceeded smoothly, resulting in 85% yield of **26** (entry 6); such a reaction would likely fail using arene sources other than diazonium salts. The benzaldehyde-derived substrate gave poor yield of **27** under the optimized conditions, with byproducts arising from acid-mediated decomposition of the substrate (entry 7). However, if the arene is separated from the alcohol by a saturated

carbon, good yield is restored, while retaining the high er apparently imparted by the steric bulk of the substituent on the saturated side of the newly-formed ketone (entry 8). *iso*-Butyl and *iso*-propyl groups in this position are tolerated (entries 9 and 10, leading to **29** and **30**), and the submission of the configurationally isomeric alkene to the reaction again resulted in isolation of the opposite enantiomer of **30** (entries 10 vs 11). A substrate with the reactive allylic alcohol group embedded in a carbon chain performs similarly to the substrates bearing vinylic methyl groups (entry 12), and a free distal alcohol does not interfere with catalysis (entry 13). An ester analogue of the free alcohol performs exceptionally well (entry 14); the alkene configuration in this case was *Z*, and the configuration of product **33** is reversed as compared to that of **32**. Finally, a substrate bearing a vinylic *n*-propyl group performs well (entry 15), and this product was prepared to compare to the entries found in Table 4.4.

Interestingly, the submission of a homoallylic alcohol substrate to the same reaction conditions as described above resulted in an exceptionally clean reaction, given the different substrate class, leading to γ-substituted ketone **35** in high enantiomeric excess (Table 4.4, entry 1). This product was isolated along with ~3% of its β-aryl ketone isomer (**34**, see Table 4.3). The products shown in Table 4.3 could conceivably arise from asymmetric Michael additions, though only one of them, **29**, was previously known. However, γ-aryl ketone products cannot be obtained using these methods, and review of the literature suggested that there was no existing methodology to deliver this type of product enantioselectively, and in a single step. A more limited scope evaluation was performed, wherein the *E*-alkene isomer of the same substrate leading to product **35** was submitted, resulting in a decreased yield of the γ-aryl ketone product, isolated with a

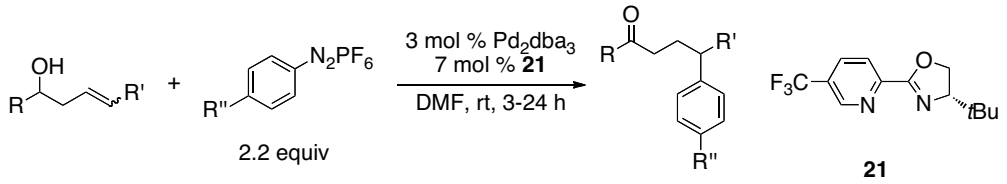
Table 4.3. Substrate scope of asymmetric Heck reaction of allylic alcohols.

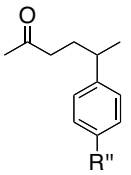
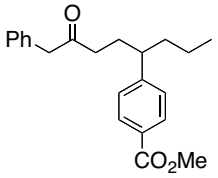


entry	product	%yield[a]	er[b]
			
1	R'' = CO_2Me, **22**	72	93:7
2	R'' = COMe, **23**	65	91:9
			
3	R'' = *p*-CO_2Me, **24**	76	97:3
4	R'' = *p*-COMe, **25**	68	97:3
5[c]	**25**	75	4:96
6[c]	R'' = *m*-I, **26**	85	3:97
7[c]	 **27**	52	3:97
8	 **28**	73	97:3
9	 **29**	67	96:4
10	 **30**	59	95:5
11[c]	**30**	77	4:96
12	 **31**	65	95:5
13	 **32**	73	94:6
14	 **33**	84	7:93
15	 **34**	74	4:96

[a]Yields are averages of two experiments performed on a scale appropriate to give a theoretical yield of >100 mg. Substrates used are (*E*)-alkenes unless otherwise noted. [b]er determined by supercritical fluid chromatography analysis using a chiral column. [c]Substrate used was (*Z*)-alkene

Table 4.4. Substrate scope of asymmetric Heck reaction of homoallylic alcohols.



entry	product	%yield[a]	er[b]
			
1[c]	R" = CO_2Me, **35**	79	96:4
2	**35**	58	10:90
3	R" = OMe, **36**	61	tbd[d]
4	R" = Me, **37**	72	97:3
5		66	6:94

[a]Yields are averages of two experiments performed on a scale appropriate to give a theoretical yield of >100 mg. Substrates used are (*E*)-alkenes unless otherwise noted. [b]er determined by supercritical fluid chromatography analysis using a chiral column. [c]Substrate used was (*Z*)-alkene.

greater amount of the β-aryl ketone isomer (approximately 14%). The product was delivered in the opposite configuration (entry 2), but in significantly lower er, suggesting that (*E*)-alkenes are poorer substrates for this reaction. An electron rich arene also added effectively to the γ position (entry 3), as did an arene bearing an alkyl group (entry 4). Finally, a more highly functionalized substrate was submitted, leading to 66% yield of product **38** (entry 5). It should be noted that all of these products are isolated along with a small amount (approximately 3-15%) of their β-aryl ketone isomers, which are not chromatographically separable. These reaction conditions are not optimized for use with homoallylic alcohols, and it is possible that future work pursuing this optimization could lead to greater yields and regio- and enantioselectivities.

Part of the mechanistic rationale used to develop the asymmetric Heck reaction of allylic alcohols invoked the inductive effect imparted by the hydroxyl group subtly biasing the alkene, resulting in favored arene attack at the β-position (Figure 4.30 a). The catalyst then selects for a carbinol hydrogen preferentially over a benzylic hydrogen, in the β-hydride elimination step. If homoallylic alcohol substrates are used, the inductive effect would be reversed according to this analysis (Figure 4.30 b), and the insertion step leading to **I** may be predicted to fail or lead to undesired regioisomers. Additionally, in order to deliver the ketone product after undergoing this insertion event, the catalyst must select for a relatively "non-hydridic" hydrogen at the saturated carbon over the more hydridic benzylic hydrogen in intermediate **I**. It then must reinsert into the disubstituted olefin to give **K**, and subsequently β-hydride eliminate a carbinol hydrogen. All of these mechanistic requirements would seem to place unreasonably high demands on the catalyst, selective as it may be. While the reaction performs surprisingly well when homoallylic alcohols are used, at this time, the success is not currently well-understood in mechanistic terms.

The next obvious question was whether the alcohol could be moved an additional carbon away from the alkene, and still result in a successful, enantioselective Heck reaction resulting in δ-substituted carbonyl products. This question also provided an opportunity for a simple mechanistic probe determining whether the steric bulk of the allylic alcohol determines enantiomeric excess. If so, submission of crotyl alcohol should result in delivery of the β-aryl aldehyde with lower er, given the small size of the primary alcohol. The C_5 and C_6 homologues may give γ- and δ-aryl aldehydes in relatively higher er, because the catalyst would presumably bind to a bulkier olefin. This was the working

hypothesis, based upon the relatively higher enantioselectivities observed when using alcohols bearing groups larger than methyl in this position (see Table 4.3). In an attempt to find answers to both of these questions, a series of primary alcohols was submitted to the reaction conditions, where the alcohol was in allylic, homoallylic and *bis*-homoallylic positions. Submission of the allylic alcohol led to relatively clean β-aryl aldehyde product **39** (Figure 4.31) with low enantiomeric excess. Submission of the homoallylic alcohol resulted in product **40**, as a mixture with regioisomeric products (~40% by GC analysis), and the *bis*-homoallylic-derived product, **41**, was isolated with a similar amount of the regioisomeric product. For the γ-aryl aldehyde product, the enantiomeric ratio was higher than the crotyl alcohol-derived product, lending some credence to the working hypothesis.

Given the discrepancy in the regioselectivity of the reactions used to prepare **40** as compared to **35**-**38**, it appears that primary alcohols are poor substrates for this reaction. Thus, it seemed possible that the poor regioselectivity of the reaction leading to **41** was a result of the primary alcohol, rather than the position of the olefin. Therefore, substrate **42**, bearing a secondary alcohol, was submitted to the enantioselective Heck reaction to evaluate this hypothesis. The reaction gave δ-substituted ketone **43** in high enantiomeric exces and improved regioselectivity (20% γ-aryl isomer) as compared to the reaction leading to 41 (40% γ-aryl isomer) (Figure 4.32). It is not clear, at this time, why the submission of primary alcohols should lead to inferior regioselectivity in the migratory insertion step.

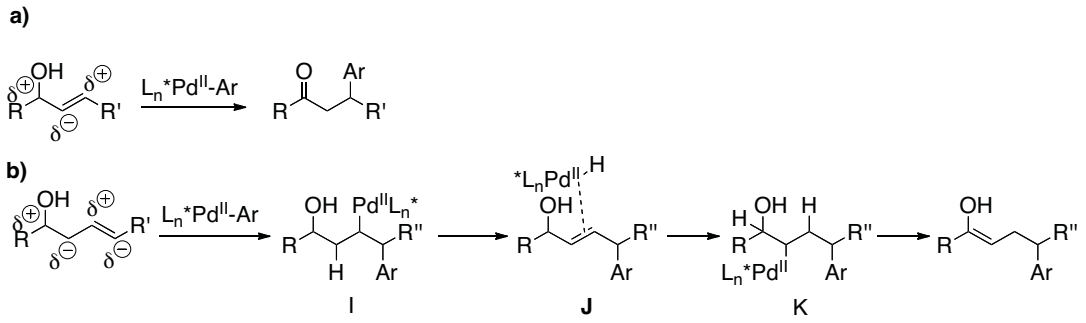
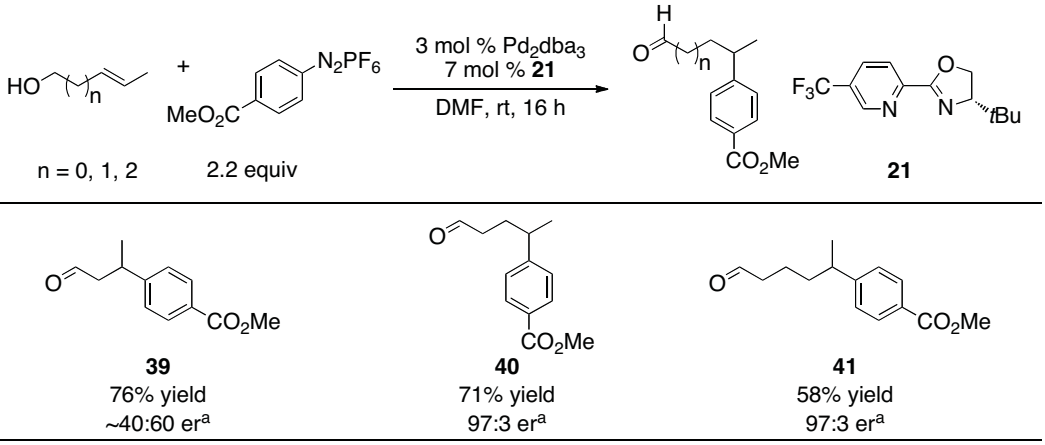


Figure 4.30. a) Mechanistic rationale predicting success using allylic alcohols. **b)** The same analysis predicts failure using homoallylic alchols.



[a]Yields are averages of two experiments performed on 0.5 mmol scale. er determined by supercritical fluid chromatography using a chiral column. er determined on samples of corresponding alcohols following $NaBH_4$ reduction.

Figure 4.31. Results using a series of primary alcohols with alkenes 0, 1, and 2 carbons away.

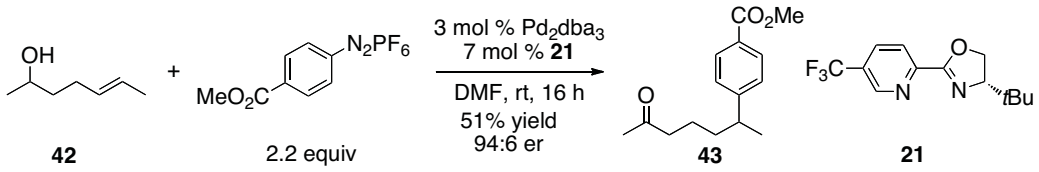


Figure 4.32. Results using a secondary alcohol substrate with the alkene 2 carbons away.

Preliminary results in the development of an enantioselective oxidative Heck reaction

Given the proposed similarity between the electrophilicities of the catalysts employed in the oxidative and classical Heck reactions described in Chapters 2 and 3, respectively, it was thought that an enantioselective oxidative Heck reaction could be developed by using a Pd^{II} catalyst in conjunction with organoboronic acid derivatives. Preliminary results indicate that this is indeed the case (Figure 4.33), where similar yields and ers are observed using the same 5-CF_3Pyr*t*Box ligand employed in the classical Heck reaction described above. The development of this reaction remains in its preliminary stages, but the distinctive synthetic appeal should compel future graduate students to continue investigation. The motivation for the further development of the oxidative variant arises from the availability of alkyl-, vinyl-, propargyl-, and heteroaromatic-boronic acid derivatives, while these electrophiles are not available in the form of diazonium salts. The successful development of an enantioselective oxidative Heck variant capable of introducing these diverse organic components would provide an immensely powerful synthetic tool for the construction of optically active ketone products with functionality in the β- and γ-positions.

Outlook and Conclusions

The recent discovery that catalyst-controlled β-hydride elimination is possible raises fascinating mechanistic questions as to the relative hydridic nature of various types of hydrogen atoms. The methodologies described in Chapters 2-4 could be reasonably viewed as "pragmatic byproducts" of theoretical studies focusing on how cationic

palladium catalysts distinguish between hydrogen atoms in different electronic and steric environments. The enantioselective Heck reaction, in particular, should be viewed as a preliminary mechanistic study, as it is reliant on the electronically competitive natures of carbinol and benzylic hydrogens, and the likely irreversible nature of β-hydride elimination events resulting in enols. These are recent discoveries and the resulting method is based on an improved understanding of a single, simple rule: namely that carbinol and benzylic hydrogens interact competitively with cationic palladium catalysts. It is not difficult to imagine that, as a greater number of these "rules" become identified and more well-understood, powerful methodologies will naturally evolve from the increased understanding. For example, it is not yet known, but is certainly conceivable that hydrogens present on the same carbon as a nitrogen group could also compete with benzylic hydrogens for the attention of the catalyst. If this is the case, it would lead to a method capable of preparing enantioenriched β-aryl imines or enamines like **42** and **43** (Figure 4.34 a). A halogen could also conceivably provide subtle electronic bias to an adjacent olefin, and the submission of these substrates could lead to enantioenriched vinyl halides, **44** (Figure 4.34 b). It is also possible that the Pd-catalyst could "walk" through distal stereocenters en route to an irreversible β-hydride elimination event to deliver enols, which would tautomerize to products like **45** (Figure 4.34 c). The result ofthis transformation would be to simultaneously install an arene in enantioselective fashion, and oxidize a distal alcohol, without racemizing stereocenters along the way. These possibilities are in addition to the prospect of installing nonaromatic or heteroaromatic nucleophiles as discussed above. In short, the outlook for the development of exciting new methodology by gaining mechanistic understanding appears

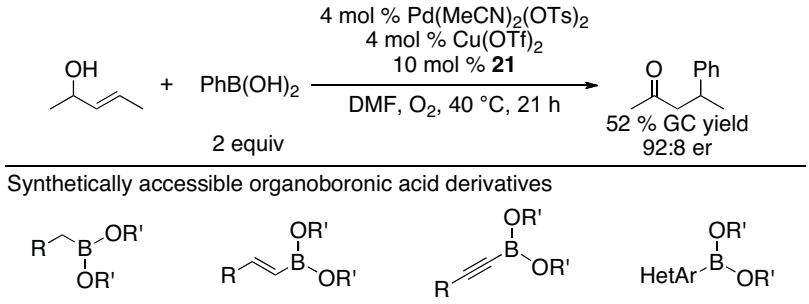


Figure 4.33. Preliminary results of an enantioselective oxidative Heck reaction, and synthetically accessible organoboronic acid derivatives.

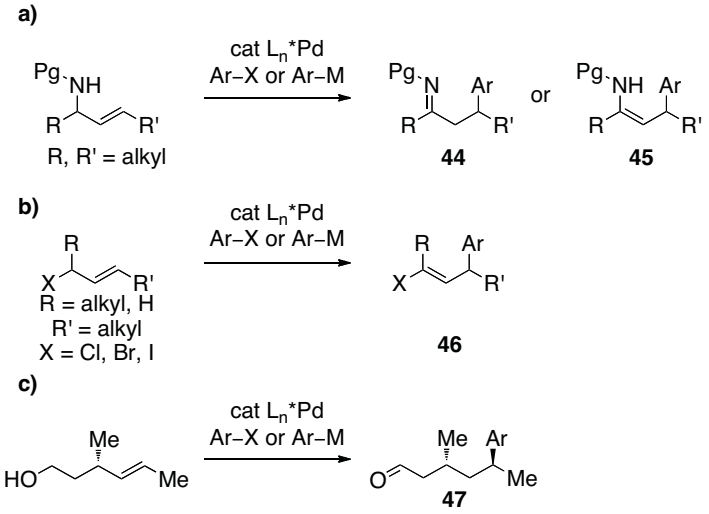


Figure 4.34. Future mechanistic experiments probing the relative hydridic nature of various types of protons, namely **a)** those adjacent to a nitrogen atom, and **b)** those adjacent to a halogen, and resulting potential methodologies. **c)** Simultaneous enantioselective functionalization of an alkene, and oxidation of an alcohol without racemizing an intervening stereocenter.

to be exceptionally bright, and several students in the Sigman laboratory are currently investigating these questions.

Conclusions

In summary, an enantioselective Heck reaction of acyclic alkene substrates has been developed, which relies upon the competitive electronic natures of benzylic and

carbinol hydrogen atoms. This transformation is the first example of an asymmetric,transition-metal-catalyzed reaction employing aryldiazonium salts, and may inspire future employment of these useful reagents in diverse asymmetric catalytic reactions. The initial goals of the project focused on the use of allylic alcohol substrates, since the migratory insertion event results in the direct delivery of a Pd^{II}-alkyl species, which mustdistinguish between these carbinol and benzylic hydrogens. The resulting methodology is demonstrably more tolerant of functional groups than competing asymmetric Michael addition chemistry. Surprisingly, the submission of homoallylic alcohol substrates results in the formation of enantioenriched γ-aryl ketones, which are not directly accessible via any known one-step procedure. The regioselectivity of this transformation suffers somewhat, but future optimization focused on this substrate class may solve this problem. A similar transformation under oxidative conditions is currently in development, and could potentially lead to methods enabling the asymmetric synthesis of β-alkyl, β-vinyl, β-propargyl, and β-heteroaryl ketones, and possibly their γ-substituted analogues. The communities' understanding of what types of hydrogen atoms interact competitively with cationic palladium catalysts is relatively limited at this stage, and it is anticipated that future useful methodology will by the byproduct of increased understanding.

Experimental

General considerations

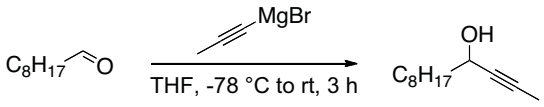
Dry dimethylacetamide (DMA), and dimethylformamide (DMF) were purchased from Aldrich and stored over activated 3 angstrom molecular sieves (3 Å MS).

Tetrahydrofuran (THF) and dichloromethane (DCM) were dried before use by passing through a column of activated alumina. Alkene substrates were purchased from Aldrich, TCI or Acros, or synthesized according to the procedures referenced. Aldehyde precursors to alkene substrates were purchased from Aldrich. Propargyl magnesium bromide was purchased from Aldrich. Alkyne precursors to alkene substrates were purchased from Aldrich. Aniline precursors to aryldiazonium tetrafluoroborates and hexafluorophosphates were purchased from Aldrich. Palladium(II) chloride was purchased from Pressure Chemicals. Pd_2dba_3 was synthesized according to the literature procedure.[97] Picolinic acid derivatives were purchased from Aldrich or Matrix scientific. Amino alcohols were synthesized according to the literature procedure. ^{1}H-NMR spectra were obtained at 300 MHz or 400 MHz, chemical shifts are reported in ppm, and referenced to the $CHCl_3$ singlet at 7.26 ppm. ^{13}C-NMR spectra were obtained at 75 MHz or 100 MHz and referenced to the center peak of the $CDCl_3$ triplet at 77.23 ppm. The abbreviations s, d, t, quint, dd, dt, and m stand for the resonance multiplicities singlet, doublet, triplet, quintet, doublet of doublets, doublet of triplets and multiplet, respectively. Thin-layer chromatography was performed with EMD silica gel 60 F254 plates eluting with solvents indicated, visualized by a 254 nm UV lamp and stained with phosphomolybdic acid. Flash chromatography was performed using EM reagent silica 60 (230-400 mesh). IR spectra were recorded using a Thermo Nicolet FT-IR. High resolution mass spectrometry (HRMS) data were obtained on a Waters LCP Premier XE instrument by ESI/TOF. All previously unknown compounds have been submitted to HRMS analysis, but data has not yet been received. Achiral GC (gas chromatography) was performed using a Hewlett Packard HP 6890 series GC system fitted with an Agilent

HP-5 column. Chiral GC analysis was performed using a Hewlett Packard HP 6890 Series CG system fitted with a HP-Chiral permethylated β-cyclodextrin column. SFC (supercritical fluid chromatography) analysis was performed at 40 ºC, using a Thar instrument fitted with an AD-H or AS-H column. Optical rotations were measured (Na D line) on a Perkin Elmer Model 343 Polarimeter fitted with a micro cell with a 1 dm path length; concentrations are reported in g/100 mL. It should be noted that while no incident occurred during this study, aryldiazonium salts can be explosive. (*S*)-(+)-**29** Was a previously known compound with a known optical rotation,[98,99] and the absolute stereochemistry of products **22**-**34** were assigned based on analogy to this compound where possible.

General procedure for the synthesis of propargylic alcohol precursors to allylic alcohol substrates

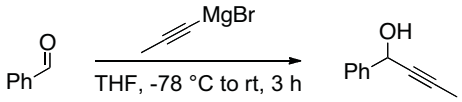
Dodec-2-yn-4-ol



To a dry 100 mL round-bottom flask containing a stir bar was added nonanal (1.42 g, 10 mmol). The flask was placed under an N_2 atmosphere, and cooled to -78 ^{o}C. A solution of 1-propynyl magnesium bromide (22 mL, 0.5 M in THF, 1.1 equiv) was added slowly while stirring. The mixture was stirred at that temperature for 1 h, prior to allowing it to warm to room temperature, and stirring for an additional 2 h. Saturated ammonium chloride (20 mL) was added slowly, prior to transferring the mixture to a 250 mL separatory funnel with diethyl ether. The aqueous layer was extracted with ether (3 x 50 mL). The combined organic layers were washed with water (1 x 50 mL), then brine,

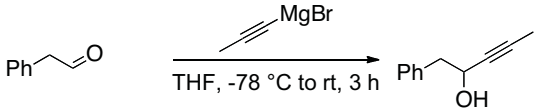
and then dried over sodium sulfate. The organic mixture was concentrated under reduced pressure, and the concentrate was purified by silica gel flash chromatography using 5% acetone in hexanes to give dodec-2-yn-4-ol as a colorless oil (1.24 g, 68%). The purity was confirmed by ^{1}H NMR.[100]

1-Phenylbut-2-yn-1-ol



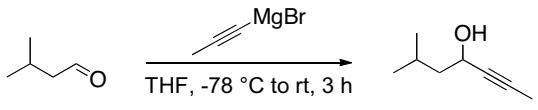
The procedure used for the preparation of dodec-2-yn-4-ol was used except benzaldehyde (1.06 g, 10 mmol) was used. The product was purified by silica gel chromatography using 5% acetone in hexanes to give 1-phenylbut-2-yn-1-ol (1.41 g, 97%). The purity was confirmed by ^{1}H NMR.[101]

1-Phenylpent-3-yn-2-ol



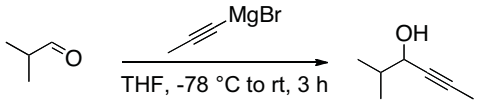
The procedure used for the preparation of dodec-2-yn-4-ol was used except 2-phenylacetaldehyde (1.20 g, 10 mmol) was used. The product was purified by silica gel chromatography using 5% acetone in hexanes to give 1-phenylpent-3-yn-2-ol (1.04 g, 65%). The purity was confirmed by ^{1}H NMR.[102]

6-Methylhept-2-yn-4-ol



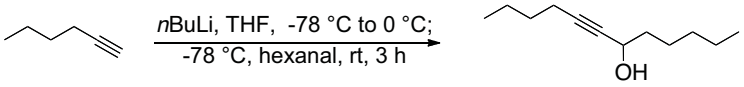
The procedure used for the preparation of dodec-2-yn-4-ol was used except 3-methybutanal (860 mg, 10 mmol) was used. The product was purified by silica gel chromatography using 3% acetone in hexanes to give 6-methylhept-2-yn-4-ol (810 mg, 64%). The purity was confirmed by ^{1}H NMR.[103]

2-Methylhex-4-yn-3-ol



The procedure used for the preparation of dodec-2-yn-4-ol was used except isobutyraldehyde (360 mg, 5 mmol) was used. The product was purified by silica gel chromatography using 3% acetone in hexanes to give 6-methylhex-4-yn-2-ol (380 mg, 68%). The purity was confirmed by ^{1}H NMR.[104]

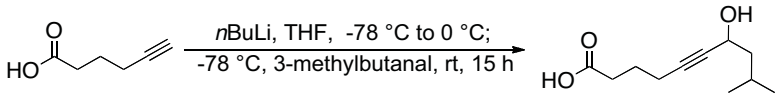
Synthesis of dodec-7-yn-6-ol



To a dry 100 mL round-bottom flask containing a stir bar and under an N_2 atmosphere was added THF (15 mL). The solvent was cooled to -78 ^{o}C, prior to adding 1-hexyne via syringe (870 μL, 620 mg, 7.5 mmol). To this mixture was added *n*BuLi (3.2 mL of 2.5 M solution in THF, 8.0 mmol, 1.1 equiv) via syringe. The mixture was allowed to warm to 0 ^{o}C, and stirred at that temperature for 1 h. The mixture was then cooled to -78 ^{o}C, and to this mixture hexanal (930 μL, 650 mg, 7.5 mmol) was added dropwise via syringe. The mixture was allowed to warm to room temperature, and stirred for 3 h. Saturated ammonium chloride (15 mL) was added slowly, prior to transferring the

mixture to a 250 mL separatory funnel with diethyl ether. The aqueous layer was extracted with ether (3 x 40 mL). The combined organic layers were washed with water (1 x 40 mL), then brine (1 x 40 mL), and then dried over sodium sulfate. The organic mixture was concentrated under reduced pressure, and the concentrate was purified by silica gel flash chromatography using 2% acetone in hexanes to give dodec-7-yn-6-ol as a colorless oil (980 mg, 72% yield). Purity was confirmed by ^{1}H NMR.[105]

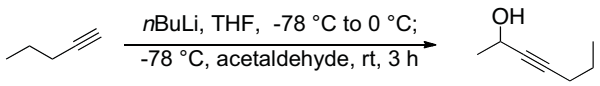
Synthesis of 7-hydroxy-9-methyldec-5-ynoic acid



To a dry 100 mL round-bottom flask containing a stir bar was added 560 mg hex-5-ynoic acid (560 mg, 5 mmol). The flask was placed under an N_2 atmosphere, prior to adding THF (50 mL) and cooling the mixture to -78 ^{o}C. To the cooled solution was added *n*BuLi (5 mL of a 2.5 M solution in hexanes, 11 mmol, 2.2 equiv) dropwise via syringe. The mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was cooled to -78 ^{o}C, and then to this mixture 3-methylbutanal (600 μL, 470 mg, 5.5 mmol, 1.1 equiv) was added dropwise via syringe. The mixture was allowed to warm to room temperature, and stirred for 15 h. Saturated ammonium chloride (15 mL) was added slowly, prior to transferring the mixture to a 250 mL separatory funnel with diethyl ether. The aqueous layer was extracted with ether (3 x 40 mL). The combined organic layers were washed with water (1 x 40 mL), then brine (1 x 40 mL), and then dried over sodium sulfate. The organic mixture was concentrated under reduced pressure, and the concentrate was purified by silica gel flash chromatography using 20% acetone in

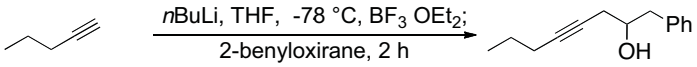
hexanes to give 7-hydroxy-9-methyldec-5-ynoic (800 mg) with minor impurities. This mixture was carried forward without further purification.

Synthesis of hept-3-yn-2-ol



The procedure used for the preparation of dodec-7-yn-6-ol was followed except 1-pentyne (990 μL, 680 mg, 10 mmol) and acetaldehyde (620 μL, 480 mg, 11 mmol) were used. The product was purified by silica gel chromatography using 5% acetone in hexanes to give hept-3-yn-2-ol (670 mg, 60%). The purity was confirmed by ^{1}H NMR.[106]

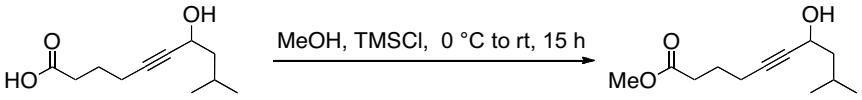
Synthesis of 1-phenyloct-4-yn-2-ol



A dry 50 mL round bottom flask containing a stir bar was placed under an N_2 atmosphere prior to adding THF (10 mL). The solvent was cooled to -78 ^{o}C, and to it was added 1-pentyne (740 μL, 510 mg, 7.5 mmol). To this mixture was added *n*BuLi (3.0 mL of a 2.5 M solution in hexanes, 7.5 mmol) dropwise via syringe. To this mixture was added borontrifluoride etherate (930 μL, 7.5 mmol) dropwise via syringe, and the resulting mixture was stirred for 30 min. To this mixture was added 2-benzyloxirane (810 μL, 1.00 g, 7.5 mmol), and the resulting mixture was stirred for 2 h. Saturated ammonium chloride (15 mL) was added slowly, prior to transferring the mixture to a 250 mL separatory funnel with diethyl ether. The aqueous layer was extracted with ether (3 x 40 mL). The combined organic layers were washed with water (1 x 40 mL), then brine (1

x 40 mL), and then dried over sodium sulfate. The organic mixture was concentrated under reduced pressure, and the concentrate was purified by silica gel flash chromatography using hexanes to 5% acetone in hexanes to give 1-phenyloct-4-yn-2-ol (1.26 g) with minor impurities. This mixture was carried forward without further purification.

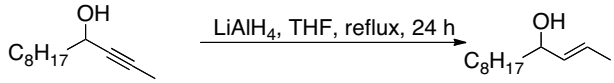
Synthesis of methyl 7-hydroxy-9-methyldec-5-ynoate



To a dry 25 mL round-bottom flask containing a stir bar was added 7-hydroxy-9-methyldec-5-ynoic (570 mg, 2.9 mmol). The flask was placed under an N_2 atmosphere, prior to add methanol (2 mL). The mixture was cooled to 0 ^{o}C, and to the cooled mixture was added chlorotrimethylsilane (560 uL, 480 mg, 4.4 mmol, 1.5 equiv). The mixture was allowed to warm to room temperature, and stirred for 15 h. The solvent was removed under reduced pressure, resulting in a yellow oil. The residue was transferred to a separatory funnel using 50 mL diethyl ether. The organic mixture was washed with water (3 x 10 mL), then brine (1 x 10 mL), and was then dried over sodium sulfate. The organic layer was concentrated under reduced pressure to give a light yellow oil (620 mg), which was carried forward without purification.

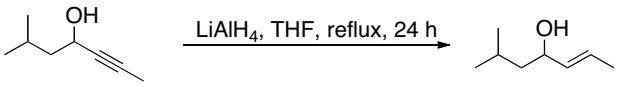
<u>General procedure for the synthesis of (*E*)-allylic alcohol substrates</u>

Synthesis of (*E*)-dodec-2-en-4-ol



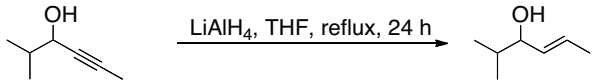
To a dry 100 mL round-bottom flask equipped with a stir bar was added lithium aluminum hydride (230 mg, 6 mmol, 3 equiv). The flask was equipped with a condensor, and the apparatus was placed under an N_2 atmosphere. To this flask was added THF (30 mL), and the mixture was stirred. To this mixture was slowly added dodec-2-yn-4-ol (360 mg, 2 mmol) in THF (10 mL). The mixture was heated to gentle reflux using a heating mantle, and stirred for 24 h. The mixture was cooled to 0 ^{o}C, the condensor was removed, and the mixture was diluted with diethyl ether (10 mL). To this mixture was added water (230 μL), dropwise via syringe. To the resulting mixture was added 20 wt% KOH (230 μL), then water (690 μL). This mixture was stirred for 1 h, then placed in a sonicating water bath for an additional 1 h. The mixture was then filtered through Celite, and the resulting homogeneous organic solution was concentrated under reduced pressure. The mixture was purified by silica gel flash chromatography using 2% acetone in hexanes to give (*E*)-dodec-2-en-4-ol (260 mg, 69%). The purity was confirmed by ^{1}H NMR.[107]

Synthesis of (*E*)-6-methylhept-2-en-4-ol



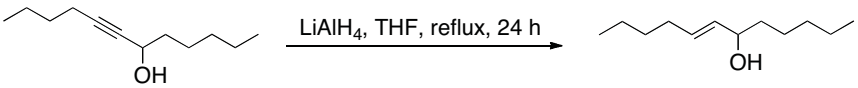
The procedure used for the preparation of (*E*)-dodec-2-en-4-ol was followed except 6-methylhept-2-yn-4-ol (250 mg, 2 mmol) was used. The product was purified by silica gel flash chromatography using 2% acetone in hexanes to give (*E*)-6-methylhept-2-en-4-ol (95 mg, 37%). The purity was confirmed by ^{1}H NMR.[108]

Synthesis of (*E*)-2-methylhex-4-en-3-ol



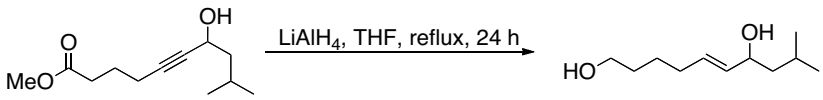
The procedure used for the preparation of (*E*)-dodec-2-en-4-ol was followed except 2-methylhex-4-yn-3-ol (330 mg, 2.9 mmol) was used. The product was purified by silica gel flash chromatography using 2% acetone in hexanes to give (*E*)-2-methylhex-4-en-3-ol (180 mg, 54%). The purity was confirmed by ^{1}H NMR.[109]

Synthesis of (*E*)-dodec-7-en-6-ol



The procedure used for the preparation of (*E*)-dodec-2-en-4-ol was followed except dodec-7-yn-6-ol (540 mg, 3.0 mmol) was used. The product was purified by silica gel flash chromatography using 2% acetone in hexanes to give (*E*)-dodec-7-en-6-ol (420 mg, 76%). The purity was confirmed by ^{1}H NMR.[110]

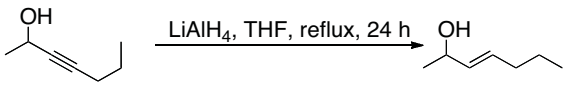
Synthesis of (*E*)-9-methyldec-5-ene-1,7-diol



The procedure used for the preparation of (*E*)-dodec-2-en-4-ol was followed except methyl-7-hydroxy-9-methyldec-5-ynoate (370 mg, 1.7 mmol), and 330 mg $LiAlH_4$ (8.8 mmol 5.0 equiv) were used. The product was purified by silica gel flash chromatography using 10% acetone in hexanes to give (*E*)-9-methyldec-5-ene-1,7-diol (280 mg, 86%) as a colorless oil. R_f = 0.31 w/ 20% acetone:hexanes. ^{1}H-NMR (300

MHz, $CDCl_3$) δ = 5.69-5.60 (m, 1 H), 5.51-5.43 (m, 1 H), 4.16-4.08 (m, 1 H), 3.65 (q, *J* = 6.2 Hz, 2 H), 2.08 (dt, *J* = 7.3, 6.7 Hz, 2 H), 1.76-1.21 (m, 8 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 0.91 (d, *J* = 6.6 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 134.0, 131.6, 71.5, 63.0, 46.7, 32.4, 32.1, 25.5, 24.8, 23.1, 22.7. IR (neat): 3313, 2953, 2929, 2968, 1467, 1366, 1056, 968 cm^{-1}. HRMS $C_{11}H_{22}O_2$ $(M+Na)^+$ calcd. 209.1517, obsvd. 209.1520.

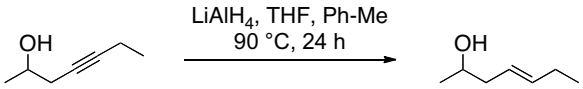
Synthesis of (*E*)-hept-3-en-2-ol



The procedure used for the preparation of (*E*)-dodec-2-en-4-ol was followed except hept-3-yn-2-ol (1.84 g, 16.4 mmol) was used. The product was purified by silica gel flash chromatography using 2% acetone in hexanes to give (*E*)-hept-3-en-ol (330 mg, 29%). The purity was confirmed by ^{1}H NMR.[111]

General procedure for the synthesis of (*E*)-homoallylic alcohol substrates

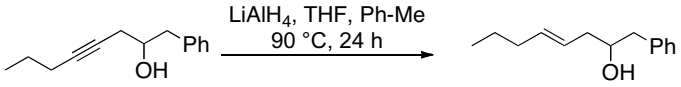
Synthesis of (*E*)-hept-4-en-2-ol



To a dry 100 mL round-bottom flask equipped with a stir bar was added lithium aluminum hydride (1.20 g, 32 mmol, 3.2 equiv). The flask was equipped with a condensor, and the apparatus was placed under an N_2 atmosphere. To this flask was added toluene (13 mL), and THF (6 mL) and the mixture was stirred. To this mixture was slowly added hept-4-yn-2-ol (1.12 g, 10 mmol) in THF (7 mL). The mixture was heated to 90 ^{o}C, using a temperature-regulated oil bath, and stirred for 24 h. The mixture was

cooled to 0 °C, the condensor was removed, and the mixture was diluted with diethyl ether (20 mL). To this mixture was added water (1.2 mL), dropwise via syringe. To the resulting mixture was added 20 wt% KOH (1.2 mL), then water (3.6 mL). This mixture was stirred for 1 h, then placed in a sonicating water bath for an additional 1 h. The mixture was then filtered through Celite, and the resulting homogeneous organic mixture was concentrated under reduced pressure to give a mixture containing toluene. The mixture was purified by silica gel flash chromatography using 0% to 10% to 20% diethyl ether in pentane to give (*E*)-hept-4-en-2-ol (760 mg, 67%). The purity was confirmed by ^{1}H NMR.[112]

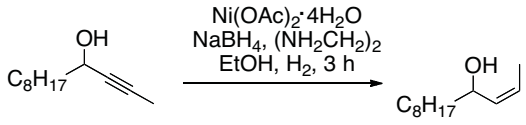
Synthesis of (*E*)-1-phenyloct-4-en-2-ol



The procedure used for the preparation of (*E*)-hept-4-en-2-ol was followed except 1-phenyloct-4-yn-2-ol (400 mg, 2 mmol) was used. The product was purified by silica gel flash chromatography using 0 to 3% acetone in hexanes to give (*E*)-1-phenyloct-4-en-2-ol (240 mg, 59%) as a colorless oil. R_f = 0.34 w/ 10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.34-7.21 (m, 5 H), 5.61-5.52 (m, 1 H), 5.49-5.39 (m, 1 H). 3.88-3.78 (m, 1 H), 2.84-2.68 (m, 2 H), 2.32-2.10 (m, 2 H), 2.01 (dt, *J* = 7.3, 6.6 Hz, 2 H), 1.70 (d, *J* = 3.4 Hz, 1 H), 1.39 (sextet, *J* = 7.4 Hz, 2 H), 0.90 (t, *J* = 7.3 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 138.8, 134.7, 129.6, 128.6, 126.6, 126.0, 72.2, 43.4, 40.2, 35.0, 22.7, 13.9. IR (neat): 3933, 3027 2956, 2925, 1496, 1436, 1078, 970, 741, 699 cm^{-1}. HRMS $C_{14}H_{20}O$ $(M+Na)^+$ calcd. 227.1412, obsvd. 227.1411.

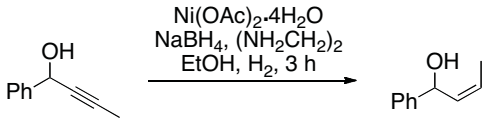
General procedure for the synthesis of (*Z*)-allylic alcohol and (*Z*)-homoallylic alcohol substrates

Synthesis of (*Z*)-dodec-2-en-4-ol



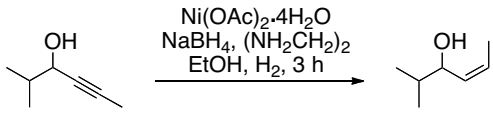
The 95:5 by weight mixture of ethanol and water that was used as solvent was prepared by diluting absolute ethanol (95 g) with water (5 g). To a 50 mL Schlenk flask containing a stir bar was added nickel(II) acetate tetrahydrate (124 mg, 0.5 mmol, 25 mol %), and sodium borohydride (20 mg, 0.5 mmol, 25 mol %). To this mixture was added 95 wt% ethanol (15 mL), and the mixture was stirred for 10 min. To this mixture was added ethylenediamine (80 mL, 1 mmol, 50 mol%) via syringe. A three-way joint was fitted with a balloon of H_2 and attached to the flask. The apparatus was evacuated and refilled with hydrogen three times. The mixture was stirred under H_2 atmosphere for 10 min. To the mixture was added dodec-2-yn-4-ol (360 mg, 2.0 mmol) in 95 wt% ethanol (5 mL). The mixture was stirred at room temperature for 3 h, before it was filtered through Celite with diethyl ether. The resulting homogeneous mixture was transferred to a separatory funnel using ether (10 mL) and water (10 mL). The aqueous layer was extracted with ether (3 x 15 mL), and the combined organic layers were washed with water (3 x 15 mL), then brine (1 x 15 mL). The combined organic layers were dried over sodium sulfate, before they were concentrated under reduced pressure. The mixture was purified by silica gel flash chromatography using 2% acetone in hexanes to give (Z)-dodec-2-en-4-ol (260 mg, 69%). The purity was confirmed by ^{1}H NMR.[107]

Synthesis of (*Z*)-1-phenylbut-2-en-1-ol



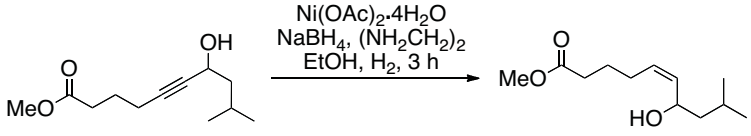
The procedure used for the preparation of (*Z*)-dodec-2-en-4-ol was followed except 1-phenylbut-2-yn-1-ol (290 mg, 2.0 mmol) was used. The product was purified by silica gel flash chromatography using 3% acetone in hexanes to give (Z)-1-phenylbut-2-en-1-ol (170 mg, 58%). The purity was confirmed by ^{1}H NMR.[113]

Synthesis of (*Z*)-2-methylhex-4-en-3-ol



The procedure used for the preparation of (*Z*)-dodec-2-en-4-ol was followed except 2-methylhex-4-yn-3-ol (450 mg, 4.0 mmol) was used. The product was purified by silica gel flash chromatography using 3% acetone in hexanes to give (Z)-2-methylhex-4-en-2-ol (180 mg, 39%). The purity was confirmed by ^{1}H NMR.[114]

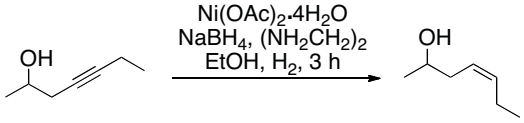
Synthesis of (*Z*)-methyl 7-hydroxy-9-methyldec-5-enoate



The procedure used for the preparation of (*Z*)-dodec-2-en-4-ol was followed except methyl 7-hydroxy-9-methyldec-5-ynoate (230 mg, 1.1 mmol) was used, and the mixture was stirred for 15 h under H_2. The product was purified by silica gel flash

chromatography using 10% acetone in hexanes to give (*Z*)-methyl 7-hydroxy-9-methyldec-5-enoate (170 mg, 72%) containing minor amounts of the (*E*)-isomer. R_f = 0.34 w/ 10% acetone in hexanes. Major isomer: ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 5.46-5.36 (m, 2 H), 4.51-4.34 (m, 1 H), 3.67 (s, 3 H), 2.33 (t, *J* = 7.3 Hz, 2 H) 2.34-2.06 (m, 2 H), 1.78-1.61 (m, 4 H), 1.55-1.46 (m, 2 H), 1.33-1.20 (m, 2 H), 0.94-0.90 (m, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 174.3, 134.5, 130.6, 65.8, 51.8, 46.7, 33.5, 27.0, 25.0, 23.2, 22.8. IR (neat): 3417, 2953, 2869, 1734, 1437, 1214, 1163, 1053, 1013. cm^{-1}. HRMS $C_{12}H_{22}O_3$ $(M+Na)^+$ calcd. 237.1467, obsvd. 237.1472.

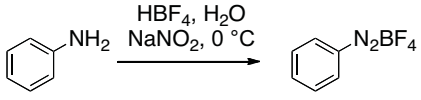
Synthesis of (*Z*)-hept-4-en-2-ol



The procedure used for the preparation of (Z)-dodec-2-en-4-ol was followed except hept-4-yn-2-ol (330 mg, 3.0 mmol) was used. The product was purified by silica gel flash chromatography using 5% diethyl ether in pentane to give (*Z*)-hept-4-en-2-ol (200 mg, 58%). The purity was confirmed by ^{1}H NMR.[115]

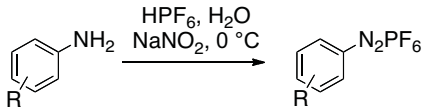
<u>Synthesis of aryldiazonium salts</u>

Synthesis of benzenediazonium tetrafluoroborate



Benzene diazonium tetrafluoroborate was synthesized by a previously reported procedure.[72]

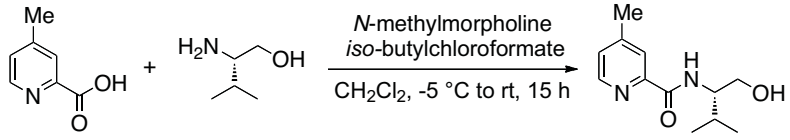
Synthesis of aryldiazonium hexafluorophosphates



Aryl diazonium hexafluorophosphate reagents were synthesized by a previously reported procedure.[116]

General procedure for the synthesis of PyrOx ligands-Anderson coupling

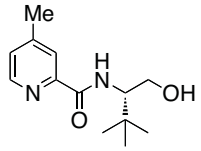
Synthesis of (*S*)-*N*-(1-hydroxy-3-methylbutan-2-yl)-4-methylpicolinamide (precursor to **13**)



To a dry 100 mL round-bottom flask containing a stir bar was added 4-methylpicolinic acid (140 mg, 1.0 mmol). The flask was placed under an N_2 atmosphere. Dichloromethane (20 mL) was added via syringe, followed by *N*-methylmorpholine (170 mL, 1.5 mmol, 1.15 equiv). The reaction mixture was cooled to 0 ^{o}C, then *iso*-butyl chloroformate was added (160 uL, 1.2 mmol, 1.2 equiv). The mixture was stirred for 20 min, then (*S*)-leucinol (120 mg, 1.2 mmol, 1.2 equiv) was added in dichloromethane (15 mL). The mixture was allowed to warm to rt and stirred for 15 h). The mixture was transferred to a separatory funnel with dichloromethane (10 mL) and water (10 mL). The aqueous layer was extracted with dichloromethane (1 x 15 mL), and the combined organic layers were washed with water (1 x 20 mL), and brine (1 x 20 mL), then dried over sodium sulfate. The dried organic mixture was concentrated under reduced pressure

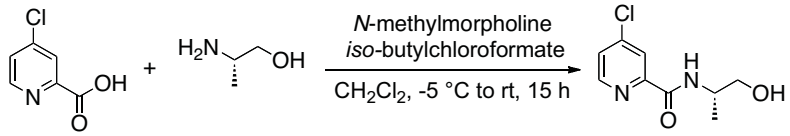
and purified by silica gel flash chromatography with 2:1 hexanes:ethyl acetate to give (*S*)-*N*-(1-hydroxy-3-methylbutan-2-yl)-4-methylpicolinamide (70 mg, 30%).

Synthesis of (*S*)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)-4-methyl picolinamide (precursor to **14**)



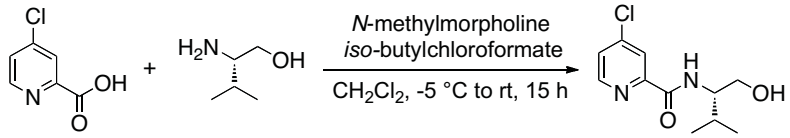
(*S*)-*N*-(1-Hydroxy-3,3-dimethylbutan-2-yl)-4-methylpicolinamide was prepared by following a literature procedure.[86]

Synthesis of (*S*)-4-chloro-*N*-(1-hydroxypropan-2-yl)picolinamide (precursor to **15**)



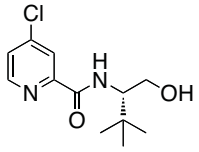
The procedure used for the preparation of (*S*)-*N*-(1-hydroxy-3-methylbutan-2-yl)-4-methylpicolinamide was used except 4-chloropicolinic acid (320 mg, 2.0 mmol) and (*S*)-alinol (140 mg, 2.4 mmol, 1.2 equiv) were used. The mixture was purified by silica gel flash chromatography with 2:1 hexanes:ethyl acetate to give (*S*)-4-chloro-*N*-(1-hydroxypropan-2-yl)picolinamide (246 mg, 58%).

Synthesis of (*S*)-4-chloro-*N*-(1-hydroxy-3-methylbutan-2-yl) picolinamide (precursor to **16**)



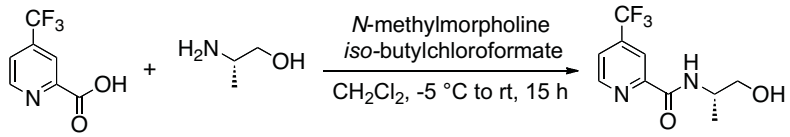
The procedure used for the preparation of (*S*)-*N*-(1-hydroxy-3-methylbutan-2-yl)-4-methylpicolinamide was used except 4-chloropicolinic acid (630 mg, 4.0 mmol) and (*S*)-leucinol (500 mg, 4.8 mmol, 1.2 equiv) were used. The mixture was purified by silica gel flash chromatography with 2:1 hexanes:ethyl acetate to give (*S*)-4-chloro-*N*-(1-hydroxy-3-methylbutan-2-yl)picolinamide (830 mg, 87%).

Synthesis of (*S*)-4-chloro-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)picolinamide (precursor to **17**)



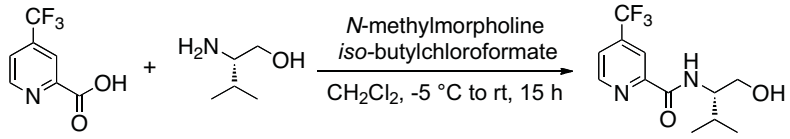
(*S*)-4-Chloro-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)picolinamide was prepared by following a literature procedure.[86]

Synthesis of (*S*)-*N*-(1-hydroxypropan-2-yl)-4-(trifluoromethyl)picolinamide (precursor to **18)**



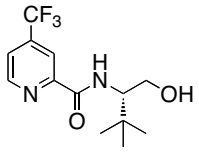
The procedure used for the preparation of (*S*)-*N*-(1-hydroxy-3-methylbutan-2-yl)-4-methylpicolinamide was used except 4-trifluoromethylpicolinic acid (380 mg, 2.0 mmol) and (*S*)-alinol (180 mg, 2.4 mmol, 1.2 equiv) were used. The mixture was purified by silica gel flash chromatography with 2:1 hexanes:ethyl acetate to give (*S*)-*N*-(1-hydroxypropan-2-yl)-4-(trifluoromethyl)picolinamide (370 mg, 75%).

Synthesis of (*S*)-*N*-(1-hydroxy-3-methylbutan-2-yl)-4-(trifluoromethyl) picolinamide (precursor to **19**)



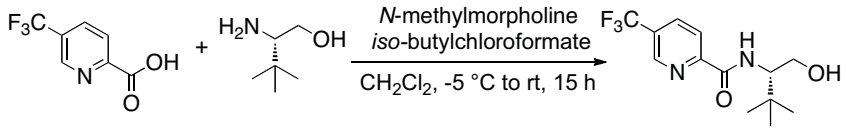
The procedure used for the preparation of (*S*)-*N*-(1-hydroxy-3-methylbutan-2-yl)-4-methylpicolinamide was used except 4-trifluoromethylpicolinic acid (380 mg, 2.0 mmol) and (*S*)-leucinol (250 mg, 2.4 mmol, 1.2 equiv) were used. The mixture was purified by silica gel flash chromatography with 2:1 hexanes:ethyl acetate to give (*S*)-*N*-(1-hydroxy-3-methylbutan-2-yl)-4-(trifluoromethyl)picolinamide (350 mg, 72%).

Synthesis of (*S*)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)-4-(trifluoromethyl) picolinamide (precursor to **20**)



(*S*)-*N*-(1-Hydroxy-3,3-dimethylbutan-2-yl)-4-(trifluoromethyl)picolinamide was prepared by following a literature procedure.[86]

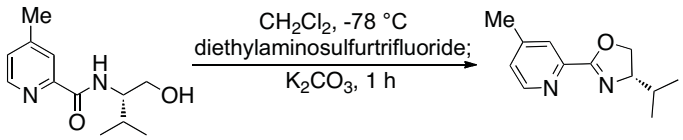
Synthesis of (*S*)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)-5-(trifluoromethyl) picolinamide (precursor to **21**)



The procedure used for the preparation of (*S*)-*N*-(1-hydroxy-3-methylbutan-2-yl)-4-methylpicolinamide was used except 5-trifluoromethylpicolinic acid (280 mg, 1.5 mmol) and (*S*)-*tert*-leucinol (190 mg, 1.6 mmol, 1.1 equiv) were used. The mixture was purified by silica gel flash chromatography with 2:1 hexanes:ethyl acetate to give (*S*)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)-5-(trifluoromethyl)picolinamide (410 mg, 94%). $[\alpha]^{20}_{D} = -10^{o}$ (c = 0.113, $CHCl_3$). R_f = 0.14 w/ 2:1 hexanes:EtOAc. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 8.83 (br s, 1 H), 8.31 (d, *J* = 8.1 Hz, 1 H), 8.25 (br d, *J* = 9.1 Hz, 1 H), 8.09 (dd, *J* = 8.1, 1.7 Hz, 1 H), 4.06-3.97 (m, 2 H), 3.73-3.67 (m, 1 H), 2.57 (br s, 1 H), 1.04 (s, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 164.1, 152.7, 145.4 (q, *J* = 4.0 Hz), 135.0 (q, *J* = 3.6 Hz), 129.0 (q, *J* = 33.1 Hz), 123.3 (q, *J* = 272.7 Hz), 122.4, 63.2, 60.5, 34.1, 27.1. IR (neat): 3379, 2964, 1673, 1528, 1327, 1166, 1135, 1076, 1054, 1018 cm-^{1}. HRMS $C_{13}H_{17}F_3N_2O_2$ $(M+Na)^+$ calcd. 313.1140, obsvd. 313.1147.

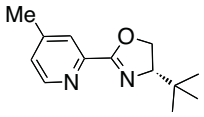
<u>General procedure for the synthesis of PyrOx ligands-oxazoline formation</u>

Figure 4.28, synthesis of (*S*)-4-isopropyl-2-(4-methylpyridin-2-yl) -4,5-dihydrooxazole (**13**)



To a dry 25 mL round-bottom flask containing a stir bar was added (*S*)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)-4-methylpicolinamide (60 mg, 0.3 mmol). The flask was placed under an N_2 atmosphere, then dichloromethane (4 mL) was added via syringe. The reaction mixture was cooled to -78 ^{o}C and diethylaminosulfur trifluoride (50 mL, 0.4 mmol, 1.4 equiv) was added. The reaction mixture was stirred for 1 h, then potassium carbonate (80 mg, 0.6 mmol, 2 equiv) was added. The mixture was warmed to rt, transferred to a separatory funnel with dichloromethane (10 mL) and water (10 mL). The organic layer was washed with saturated sodium bicarbonate (1 x 10 mL), and brine (1 x 10 mL), then dried over sodium sulfate. The dried organic layer was concentrated under reduced pressure, and the mixture purified by silica gel flash chromatography using 2:1 hexanes:ethyl acetate + 0.1% triethylamine to give the product (10 mg, 18%). This material decomposed rapidly, and was used immediately as ligand.

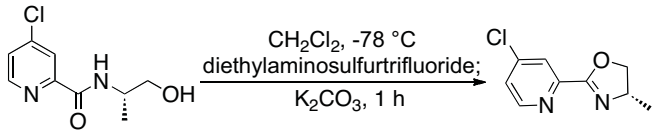
Figure 4.28, synthesis of (*S*)-4-(*tert*-butyl)-2-(4-methylpyridin-2-yl)
-4,5-dihydrooxazole (**14**)



(*S*)-*N*-(1-Hydroxy-3,3-dimethylbutan-2-yl)-4-methylpicolinamide was prepared by following a literature procedure.[86] The material decomposed rapidly, and was used immediately as ligand.

Figure 4.28, synthesis of (*S*)-2-(4-chloropyridin-2-yl)-4-methyl

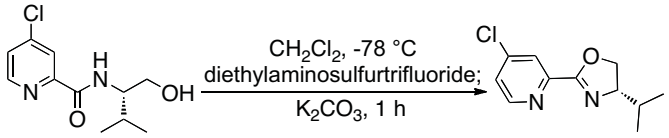
-4,5-dihydrooxazole (**15**)



The procedure used for the preparation for the preparation of (*S*)-4-isopropyl-2-(4-methylpyridin-2-yl)-4,5-dihydrooxazole was used except (*S*)-4-chloro-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)picolinamide (110 mg, 0.5 mmol) was used. The product was purified in the same fashion, to give a material (10 mg, 11%) that decomposed rapidly, and was used immediately as ligand.

Figure 4.28, synthesis of (*S*)-2-(4-chloropyridin-2-yl)-4-isopropyl

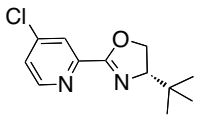
-4,5-dihydrooxazole (**16**)



The procedure used for the preparation for the preparation of (*S*)-4-isopropyl-2-(4-methylpyridin-2-yl)-4,5-dihydrooxazole was used except (*S*)-4-chloro-*N*-(1-hydroxy-3-methylbutan-2-yl)picolinamide (110 mg, 0.4 mmol) was used. The product was purified in the same fashion, to give a material (70 mg, 62%) that was used immediately as ligand.

Figure 4.28, synthesis of (*S*)-4-(*tert*-butyl)-2-(4-chloropyridin-2-yl)

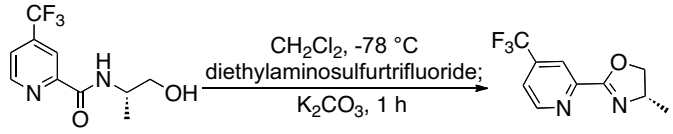
-4,5-dihydrooxazole (**17)**



S)-4-(*tert*-butyl)-2-(4-chloropyridin-2-yl)-4,5-dihydrooxazole was prepared by following a literature procedure.[86]

Figure 4.28, synthesis of (*S*)-4-methyl-2-(4-(trifluoromethyl)

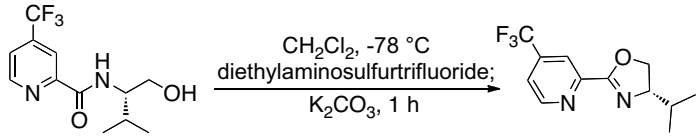
pyridin-2-yl)-4,5-dihydrooxazole (**18**)



The procedure used for the preparation for the preparation of (*S*)-4-isopropyl-2-(4-methylpyridin-2-yl)-4,5-dihydrooxazole was used except (*S*)-*N*-(1-hydroxypropan-2-yl)-4-(trifluoromethyl)picolinamide (110 mg, 0.4 mmol) was used. The product was purified in the same fashion, to give a material (32 mg, 28%) that decomposed rapidly and was used immediately as ligand.

Figure 4. 28, synthesis of (*S*)-4-isopropyl-2-(4-(trifluoromethyl)

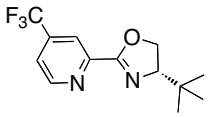
pyridin-2-yl)-4,5-dihydrooxazole (**19**)



The procedure used for the preparation for the preparation of (*S*)-4-isopropyl-2-(4-methylpyridin-2-yl)-4,5-dihydrooxazole was used except (*S*)-*N*-(1-hydroxy-3-

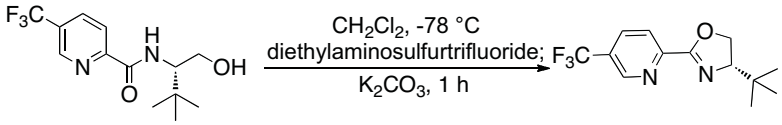
methylbutan-2-yl)-4-(trifluoromethyl)picolinamide (140 mg, 0.5 mmol) was used. The product was purified in the same fashion, to give a material (70 mg, 51%) that was used immediately as ligand.

Figure 4.28, synthesis of (*S*)-4-(*tert*-butyl)-2-(4-(trifluoromethyl) pyridin-2-yl)-4,5-dihydrooxazole (**20**)



(*S*)-4-(*tert*-Butyl)-2-(4-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole was prepared following a literature procedure.[86]

Figure 4.28, synthesis of (*S*)-4-(*tert*-Butyl)-2-(5-(trifluoromethyl) pyridin-2-yl)-4,5-dihydrooxazole (**21**)



The procedure used for the preparation for the preparation of (*S*)-4-isopropyl-2-(4-methylpyridin-2-yl)-4,5-dihydrooxazole was used except (*S*)-*N*-(1-hydroxy-3-methylbutan-2-yl)-5-(trifluoromethyl)picolinamide (290 mg, 1.0 mmol) was used. The product was purified in the same fashion, to give (*S*)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)-5-(trifluoromethyl)picolinamide (230 mg, 85%). $[\alpha]^{20}_{D} = -73^{o}$ (c = 0.100, $CHCl_3$). R_f = 0.57 w/ 2:1 hexanes:EtOAc. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 8.95 (d, *J* = 5.2 Hz, 1 H),

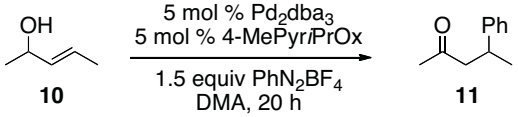
8.22 (d, *J* = 8.2 Hz, 1 H), 8.01 (ddd, *J* = 8.2, 2.3, 0.6 Hz, 1 H), 4.48 (dd, *J* = 10.3, 8.8 Hz, 1 H), 4.34 (t, *J* = 8.5 Hz, 1H), 4.16 (dd, *J* = 10.3, 8.4 Hz, 1 H), 0.98 (s, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 161.6, 150.2, 146.7 (q, *J* = 4.0 Hz) 134.0 (q, *J* = 3.6 Hz), 128.1 (q, *J* = 33.4 Hz), 123.4 (q, *J* = 272.7 Hz), 123.9, 76.9, 69.8, 34.2, 26.1. IR (neat): 2963, 1645, 1399, 1329, 1166, 1127, 1098, 1012, 668 cm^{-1}. HRMS $C_{13}H_{15}F_3N_2O$ $(M+Na)^+$ calcd. 295.1034, obsvd. 295.1038.

General procedure for the identification of optimal PyrOx ligand

in the asymmetric Heck reaction

Table 4.1, use of (*S*)-4-isopropyl-2-(4-methylpyridin-2-yl)

-4,5-dihydrooxazole (ligand **13**)



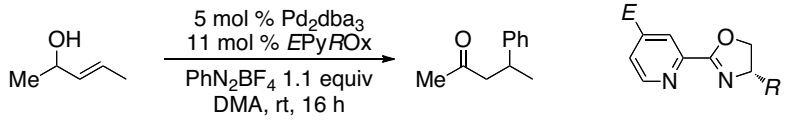
In the dry box, a 1 M solution of (*E*)-pent-3-en-2-ol (**10**), containing 10 wt% tetradecane, in DMA was prepared. To a 20 mL scintillation vial equipped with a stir bar was added benzenediasonium tetrafluoroborate (14 mg, 0.08 mmol, 1.5 equiv). To a separate vial was added Pd_2dba_3 (2 mg, 0.003 mmol, 0.05 equiv). To a separate vial was added (*S*)-4-isopropyl-2-(4-methylpyridin-2-yl)-4,5-dihydrooxazole (**13**) (1 mg, 0.006 mmol, 0.11 equiv). To the vial containing palladium was added DMA (0.25 mL), and to the vial containing the ligand was added DMA (0.20 mL). With a pipet, the mixture containing the ligand was added to the mixture containing palladium. With a pipet, the resulting mixture was perturbed several times to ensure mixing, and it was allowed to sit for 10 min. To this mixture was added 50 μL of the mixture containing the substrate and

tetradecane (0.05 mmol, 1 equiv). This mixture was added to the vial containing the aryldiazonium salt, and the vial was fitted with a lid, removed from the dry box, and stirred for 20 h. The mixture was then passed through a silica gel pipet with diethyl ether, and analyzed for product formation and enantiomeric ratio by gas chromatography. The modifications described in Table 4.1 were applied in order to identify the optimal ligand.

Table 4.2, optimization of the asymmetric Heck reaction using (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (ligand **21**)

In the dry box, to a 20 mL scintillation vial equipped with a stir bar was added benzenediazonium tetrafluoroborate (28 mg, 0.15 mmol, 1.5 equiv). To a separate vial was added Pd_2dba_3 (3 mg, 0.003 mmol, 0.03 equiv). To a separate vial was added (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (**21**) (2 mg, 0.007 mmol, 0.07 equiv). To the vial containing palladium was added DMA (0.5 mL), and to the vial containing the ligand was added DMA (0.45 mL). With a pipet, the mixture containing the ligand was added to the mixture containing palladium. With a pipet, the resulting mixture was perturbed several times to ensure mixing, and it was allowed to sit for 10 min. To this mixture was added 100 μL of the mixture containing the substrate (**10**) and tetradecane (0.1 mmol, 1 equiv). This mixture was added to the vial containing the aryldiazonium salt, and the vial was fitted with a lid, removed from the dry box, and stirred for 20 h. The mixture was then passed through a silica gel pipet with diethyl ether, and analyzed for product formation and enantiomeric ratio by gas chromatography. The modifications described in Table 4.2 were applied in order to optimize the reaction.

Table 4.1. Yield and enantiomeric ratio for the asymmetric Heck reaction of substrate **10**, using the nine-membered ligand PyrOx ligand library

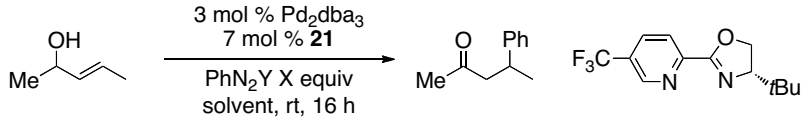


10 **11** *E*Py*R*Ox

Ligand	yield[a]	er[b]
E = Me, R = Me, **12**[c]	NA	NA
E = Me, R = *i*Pr, **13**	38.1	91.5:8.5
E = Me, R = *t*Bu, **14**	47.7	90.0:10
E = Cl, R = Me, **15**	27.3	64.0:36.0
E = Cl, R = *i*Pr, **16**	35.7	72.7:27.3
E = Cl, R = *t*Bu, **17**	58.7	90.9:8.1
E =CF_3, R = Me, **18**	25.5	63.5:35.5
E = CF_3, R = *i*Pr, **19**	43.8	70.2:29.8
E = CF_3, R = *t*Bu, **20**	57.4	91.5:8.5

[a]Yield was calculated by comparing product peak integration to integration of an internal standard using corrected GC analysis. [b]er was determined by comparing enantiomer product peak integrations using chiral GC analysis. [c]Ligand was synthetically inaccessible.

Table 4.2. Optimization of the asymmetric Heck reaction using ligand **21**

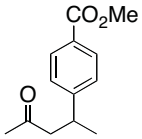


10 **11** **21**

entry	X	Y	Solvent	%conversion[a]	%yield[a]	er[b]
1	1.1	BF_4	DMA	85.6	41.2	91.2:8.8
2	1.1	BF_4	DMF	100	58.7	92.7:7.3
3	1.1	PF_6	DMF	100	41.9	93.8:6.2
4	2.2	PF_6	DMF	100	70.5	93.7:6.3

[a]Yield was calculated by comparing product peak integration to integration of an internal standard using corrected GC analysis. [b]er was determined by comparing enantiomer product peak integrations using chiral GC analysis.

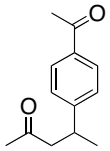
General procedure for the preparation of (*S*)-methyl 4-(4-oxopentan-2-yl) benzoate (**22**) under optimized conditions (Table 4.3, entry 1)



In the dry box, to a 25 mL round-bottom flask equipped with a stir bar was added the aryldiazonium hexafluorophosphate salt (360 mg, 1.1 mmol, 2.2 equiv) derived from methy-4-aminobenzoate. To a separate vial was added Pd_2dba_3 (14 mg, 0.02 mmol, 0.03 equiv). To a separate vial was added **21** (10 mg, 0.04 mmol, 0.07 equiv). To a separate vial was added **10** (43 mg, 0.5 mmol). To the vial containing palladium was added DMF (2 mL), to the vial containing the ligand was added DMF (2 mL), and to the vial containing the alkene was added DMF (1 mL). With a pipet, the mixture containing the ligand was added to the mixture containing palladium. With a pipet, the resulting mixture was perturbed several times to ensure mixing, and it was allowed to sit for 10 min. To this mixture was added the mixture containing the alkene. The mixture containing both the catalyst and the alkene was added to the flask containing the aryldiazonium salt, and the flask was fitted with a septum, removed from the dry box, and stirred for 3 h. The mixture was diluted with diethyl ether (10 mL) and water (10 mL). The aqueous layer was extracted with dithyl ether (2 x 15 mL). The combined organic layers were washed with water (3 x 15 mL), brine (1 x 15 mL), and dried over sodium sulfate. The dry organic solution was concentrated under reduced pressure, then purified by silica gel flash chromatography using 3 to 6% acetone in hexanes. The product was isolated as a clear oil in 71-72% yield (78 and 79 mg). $[\alpha]^{20}_{D} = +40^{o}$ (c = 0.183, $CHCl_3$). R_f = 0.25 w/ 10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 8.4

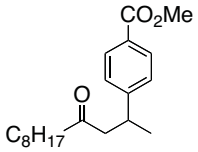
Hz, 2 H), 7.28 (d, *J* = 8.1 Hz, 2 H), 3.90 (s, 3 H), 3.37 (sextet, *J* = 7.0 Hz, 1 H), 2.73 (m, 2 H), 2.07 (s, 3 H), 1.27 (d, *J* = 6.9 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 207.4, 167.2, 151.8, 130.1, 128.5, 127.1, 52.2, 51.7, 35.5, 30.8, 21.9. IR (neat): 2958, 1712, 1610, 1435, 1256, 1163, 1110, 1018, 773, 707 cm^{-1}. HRMS $C_{13}H_{16}O_3$ $(M+H)^+$ calcd. 221.1178, obsvd. 221.1180.

Table 4.3, entry 2 ((*S*)-4-(4-acetylphenyl)pentan-2-one) (**23**)



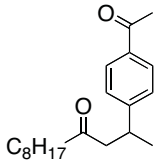
The general procedure for the preparation of **22** was used with the modifications that the aryldiazonium hexafluorophospate (330 mg 1.1 mmol, 2.2 equiv) derived from 4-aminoacetophenone was used. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 3 to 6% acetone in hexanes to give the product as a clear oil in 64-66% yield (65 mg and 67 mg). $[\alpha]^{20}_D$ = + 51^o (c = 0.113, $CHCl_3$). R_f = 0.18 w/ 10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.89 (d, *J* = 8.5 Hz, 2 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 3.38 (sextet, *J* = 7.0 Hz, 1 H), 2.82-2.65 (m, 2 H), 2.58 (s, 3 H), 2.08 (s, 3 H), 1.27 (d, *J* = 7.0 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 207.3 197.9, 152.1, 135.6, 128.9, 127.2, 51.6, 35.4, 30.8, 26.8, 22.0. IR (neat): 2963, 2928, 1713, 1677, 1603, 1415, 1358, 1267, 1163, 957, 831, 598 cm^{-1}. HRMS $C_{13}H_{16}O_2$ $(M+Na)^+$ calcd. 227.1048, obsvd. 227.1043.

Table 4.3, entry 3 ((*S*)-methyl 4-(4-oxododecan-2-yl)benzoate) (**24**)



The general procedure for the preparation of **22** was used with the following modifications. (*E*)-Dodec-2-en-4-ol (73 mg, 0.4 mmol) and the aryldiazonium hexafluorophospate (280 mg 0.9 mmol, 2.2 equiv) derived from methyl 4-aminobenzoate were used, in a total of 4 mL DMF. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 2% acetone in hexanes to give the product as a clear oil in 71-80% yield (91 mg and 102 mg). $[\alpha]^{20}_{D}$ = + 33° (c = 0.112, $CHCl_3$). R_f = 0.50 w/ 10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2 H), 3.90 (s, 3 H), 3.39 (sextet, *J* = 7.1 Hz, 1 H), 2.77-2.60 (m, 2 H), 2.38-2.20 (m, 2 H), 1.48 (pentet, *J* = 7.2 Hz, 2 H) 1.32-1.16 (m, 13 H), 0.86 (t, *J* = 7.0 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 209.8, 167.2, 152.0, 130.1, 128.4, 127.1, 52.2, 50.8, 43.7, 35.5, 32.0, 29.5, 29.3, 29.3, 23.8, 22.8, 21.9, 14.3. IR (neat): 2954, 2926, 2855, 1720, 1611, 1279, 1113, 775, 708 cm^{-1}. HRMS $C_{20}H_{30}O_3$ $(M+H)^+$ calcd. 319.2273, obsvd. 319.2272.

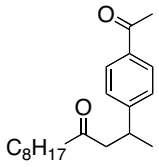
Table 4.3, entry 4 ((*S*)-2-(4-acetylphenyl)dodecan-4-one) (**25**) from (*E*)-alkene



The general procedure for the preparation of **22** was used with the following modifications. (*E*)-Dodec-2-en-4-ol (73 mg, 0.4 mmol) and the aryldiazonium

hexafluorophospate (280 mg 0.9 mmol, 2.2 equiv) derived from 4-aminoacetophenone were used, in a total of 4 mL DMF. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 2% acetone in hexanes to give the product as a clear oil in 67-68% yield (81 mg and 82 mg). $[\alpha]^{20}_{D}$ = + 28° (c = 28, $CHCl_3$). R_f = 0.44 w/ 10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.89 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 3.40 (sextet, *J* = 7.2 Hz, 1 H), 2.78-2.61 (m, 2 H), 2.58 (s, 3 H), 2.39-2.22 (m, 2 H), 1.49 (pentet, *J* = 6.8 Hz, 2 H), 1.35-1.15 (m, 13 H), 0.86 (t, *J* = 7.0 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 209.8, 197.9, 152.2, 135.6, 128.9, 127.3, 50.7, 43.7, 35.4, 32.0, 29.5, 29.3, 29.3, 26.8, 23.8, 22.8, 21.9, 14.3. IR (neat): 2956, 2925, 2824, 1713, 1682, 1610, 1557, 1414, 1358, 1267, 830, 599 cm^{-1}. HRMS $C_{20}H_{30}O_2$ $(M+H)^+$ calcd. 303.2324, obsvd. 303.2320.

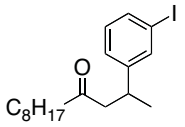
Table 4.3, entry 5 ((*R*)-2-(4-acetylphenyl)dodecan-4-one) (**25**) from (*Z*)-alkene



The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 15 mg Pd_2dba_3 (0.02 mmol, 0.04 equiv), and 10 mg ligand **21** (0.04 mmol, 0.09 equiv). (*Z*)-Dodec-2-en-4-ol (73 mg, 0.4 mmol) and the aryldiazonium hexafluorophospate (280 mg 0.9 mmol, 2.2 equiv) derived from 4-aminoacetophenone were used, in a total of 4 mL DMF. The mixture was stirred for 15 h. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 2% acetone in hexanes to give the product as a clear oil in 74-75% yield (90 mg and 92 mg). $[\alpha]^{20}_{D}$ = – 28° (c = 0.114,

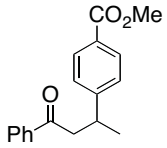
$CHCl_3$). The ^1H NMR spectrum, see below, was compared with that of the product arising from the (*E*)-isomer of the same alkene.

Table 4.3, entry 6 ((*R*)-2-(3-iodophenyl)dodecan-4-one) (**26**)



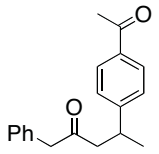
The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 13 mg Pd_2dba_3 (0.01 mmol, 0.04 equiv), and 9 mg ligand **21** (0.03 mmol, 0.09 equiv). (*Z*)-Dodec-2-en-4-ol (65 mg, 0.35 mmol) and the aryldiazonium hexafluorophospate (300 mg 0.8 mmol, 2.2 equiv) derived from 3-iodoaniline one were used, in a total of 3.5 mL DMF. The mixture was stirred for 15 h. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 1% acetone in hexanes to give the product as a yellow oil in 85-88% yield (115 mg and 119 mg). $[\alpha]^{20}_D = -21^o$ (c = 0.213, $CHCl_3$). R_f = 0.71 w/ 10% acetone in hexanes. ^1H-NMR (300 MHz, $CDCl_3$) δ = 7.55-7.50 (m, 2 H), 7.17 (d, *J* = 7.8 Hz, 1 H), 7.02 (t, *J* = 7.7 Hz, 1 H), 3.26 (sextet, *J* = 7.1 Hz, 1 H), 2.73-2.56 (m, 2 H), 2.39-2.22 (m, 2 H), 1.50 (pentet, *J* = 7.1 Hz, 2 H), 1.36-1.06 (m, 3 H), 0.87 (t, J = 7.0 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 209.8, 149.1, 136.0, 135.5, 130.4, 126.5, 94.8, 50.9, 43.8, 35.1, 32.0, 29.5, 29.3, 29.3, 23.8, 22.8, 22.0, 14.3. IR (neat): 2955, 2925, 2854, 1714, 1563, 1465, 994, 782, 696 cm^{-1}. HRMS $C_{18}H_{27}IO$ $(M+H)^+$ calcd. 387.1185, obsvd. 387.1194.

Table 4.3, entry 7 ((+)-methyl 4-(4-oxo-4-phenylbutan-2-yl)benzoate) (**27**)



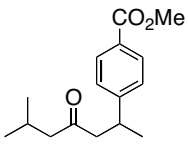
The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 14 mg Pd_2dba_3 (0.02 mmol, 0.03 equiv), and 10 mg ligand **21** (0.04 mmol, 0.07 equiv). (*Z*)-1-Phenylbut-2-en-1-ol (89 mg, 0.5 mmol) and the aryldiazonium hexafluorophospate (350 mg 1.1 mmol, 2.2 equiv) derived from methyl 4-aminobenzoate were used, in a total of 5 mL DMF. The mixture was stirred for 15 h. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 1% acetone in hexanes to give the product as a white solid in 50-53% yield (71 mg and 75 mg). As mentioned in the narrative, the use of benzylic alcohols in the asymmetric Heck reaction results in the delivery of byproducts. This product could not be fully purified, and the characterization data that follows pertains to a mixture of the desired product and unknown impurities. $[\alpha]^{20}_D$ = + 7° (c = 0.097, $CHCl_3$). R_f = 0.38 w/ 10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.98-7.90 (m, 4 H), 7.58-7.53 (m, 1 H), 7.47-7.42 (m, 2 H), 7.36-7.33 (m, 2 H). 3.59 (s, 3 H), 3.62-3.55 (m, 1 H), 3.59-3.17 (m, 2 H), 1.35 (d, *J* = 7.0 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 198.7, 167.2, 152.1, 137.2, 133.3, 130.1, 128.8, 128.2, 127.2, 120.4, 52.2, 46.7, 35.7, 22.0. IR (neat): 2953, 1716, 1684, 1610, 1435, 1276, 1111, 1000, 753, 691 cm^{-1}. HRMS $C_{18}H_{18}O_3$ $(M+H)^+$ calcd. 283.1334, obsvd. 283.1328.

Table 4.3, entry 8 ((*S*)-4-(4-acetylphenyl)-1-phenylpentan-2-one) (**28**)



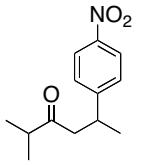
The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 10 mg Pd_2dba_3 (0.011 mmol, 0.03 equiv), and 7 mg ligand **21** (0.04 mmol, 0.07 equiv). (*E*)-1-phenylpent-3-en-2-ol (57 mg, 0.35 mmol) and the aryldiazonium hexafluorophospate (230 mg 0.8 mmol, 2.2 equiv) derived from 4-aminoacetophenone were used, in a total of 3.5 mL DMF. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 3% acetone in hexanes to give the product as a clear oil in 71-74% yield (70 mg and 73 mg). $[\alpha]^{20}_D$ = + 10° (c = 0.097, $CHCl_3$). R_f = 0.38 w/ 10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.85 (d, *J* = 8.4 Hz, 2 H), 7.33-7.21 (m, 5 H), 7.10 (dd, *J* = 8.0, 3.0 Hz, 2 H), 3.59 (s, 2 H), 3.67 (sextet, *J* = 7.1 Hz, 1 H), 2.84-2.64 (m, 2 H), 2.57 (s, 3 H), 1.21 (d, *J* = 6.9 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 206.7, 198.0, 152.0, 135.6, 133.9, 129.6, 128.9, 128.9, 127.3, 127.2, 51.0, 49.7, 35.4, 26.8, 21.8. IR (neat): 3029, 2963, 2928, 1713, 1680, 1607, 1269, 1013, 835, 702 cm^{-1}. HRMS $C_{19}H_{20}O_2$ $(M+Na)^+$ calcd. 303.1361, obsvd. 303.1362.

Table 4.3, entry 9 ((*S*)-methyl 4-(6-methyl-4-oxoheptan-2-yl)benzoate) (**29**)



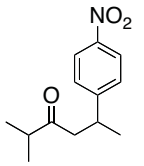
The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 10 mg Pd_2dba_3 (0.01 mmol, 0.03 equiv), and 7 mg ligand **21** (0.04 mmol, 0.07 equiv). (*E*)-6-methylhept-2-en-4-ol (45 mg, 0.35 mmol) and the aryldiazonium hexafluorophospate (240 mg 0.8 mmol, 2.2 equiv) derived from methyl 4-aminobenzoate were used, in a total of 3.5 mL DMF. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 2% acetone in hexanes to give the product as a white solid in 65-69% yield (60 mg and 63 mg). This product was the only entry in Tables 4.3-4.5 that was previously known,[98,99] and had reported the optical rotation of either enantiomer. The optical rotation reported in the literature for (*S*)- methyl 4-(6-methyl-4-oxoheptan-2-yl)benzoate (also known as *ar*-(+)-juvabione) is $[\alpha]^{27}_D$ = + 23° (concentration and solvent not provided). This value was used to assign the absolute configuration of compounds **22**-**34** by analogy. $[\alpha]^{20}_D$ = + 27° (c = 0.117, $CHCl_3$). R_f = 0.72 w/ 10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 9.1 Hz, 2 H), 3.90 (s, 3 H), 3.39 (sextet, *J* = 7.1 Hz, 1 H), 2.76-2.59 (m, 2 H), 2.26-2.00 (m, 3 H), 1.26 (d, *J* = 7.0 Hz, 3 H), 0.84 (d, *J* = 6.5 Hz, 3 H), 0.83 (d, *J* = 6.5 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 209.4, 167.2, 152.0, 130.1, 128.4, 127.1, 52.7, 52.2, 51.3, 35.4, 24.7, 22.7, 21.9. IR (neat): 2956, 2872, 1713, 1610, 1435, 1277, 1112, 1012, 856, 774, 708 cm^{-1}. HRMS $C_{16}O_{22}O_3$ $(M+H)^+$ calcd. 263.1647, obsvd. 263.1639.

Table 4.3, entry 10 ((*S*)-2-methyl-5-(4-nitrophenyl)hexan-3-one (**30**) from (*E*)-alkene)



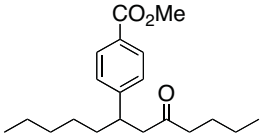
The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 14 mg Pd_2dba_3 (0.011 mmol, 0.03 equiv), and 10 mg ligand **21** (0.04 mmol, 0.07 equiv). (*E*)-2-methylhex-4-en-3-ol (57 mg, 0.5 mmol) and the aryldiazonium hexafluorophospate (330 mg 1.1 mmol, 2.2 equiv) derived from 4-nitroaniline were used, in a total of 5 mL DMF. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 4% acetone in hexanes to give the product as a clear oil in 58-59% yield (68 mg and 69 mg). $[\alpha]^{20}_{D}$ = + 24° (c = 0.100, $CHCl_3$). R_f = 0.36 w/ 10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 8.25 (d, *J* = 8.8 Hz, 2 H), 7.38, (d, *J* = 8.7 Hz, 2 H), 3.48 (sextet, *J* = 7.0 Hz, 1 H), 2.84-2.69 (m, 2 H), 2.50 (septet, *J* = 7.0 Hz, 1 H), 1.28 (d, *J* = 7.0 Hz, 3 H), 1.05 (d, *J* = 6.9 Hz, 3 H), 0.99 (d, *J* = 7.0 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 212.6, 154.5, 129.2, 128.0, 124.0, 48.3, 41.4, 35.1, 21.8, 18.2, 18.1. IR (neat): 2969, 2933, 1710, 1599, 1517, 1345, 1110, 1008, 855, 700 cm^{-1}. HRMS $C_{13}H_{17}NO_3$ $(M)^+$ calcd. 235.1208, obsvd. 235.1212.

Table 4.3, entry 11 ((*R*)-2-methyl-5-(4-nitrophenyl)hexan-3-one (**30**) from (*Z*)-alkene)



The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 18 mg Pd_2dba_3 (0.02 mmol, 0.04 equiv), and 12 mg ligand **21** (0.05 mmol, 0.09 equiv). (*E*)-Methylhex-4-en-3-ol (57 mg, 0.5 mmol) and the aryldiazonium hexafluorophospate (330 mg 1.1 mmol, 2.2 equiv) derived from 4-nitroaniline were used, in a total of 5 mL DMF. The reaction was stirred for 24 h. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 4% acetone in hexanes to give the product as a clear oil in 70-80% yield (82 mg and 94 mg). $[\alpha]^{20}_D = -24^o$ (c = 0.117, $CHCl_3$). The ^1H NMR spectrum, see below, was compared to that of the product arising from the (*E*)-isomer of the same alkene. Note that the sample was contaminated with dba; this problem will be addressed.

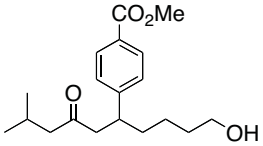
Table 4.3, entry 12 ((*S*)-methyl 4-(8-oxododecan-6-yl)benzoate) (**31)**



The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 10 mg Pd_2dba_3 (0.01 mmol, 0.03 equiv), and 7 mg ligand **21** (0.02 mmol, 0.07 equiv). (*E*)-Dodec-6-en-5-ol (65 mg, 0.35 mmol) and the aryldiazonium hexafluorophospate (240 mg 0.8 mmol, 2.2 equiv) derived from methyl 4-aminobenzoate were used, in a total of 3.5 mL DMF. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 1% acetone in hexanes to give the product as a clear oil in 61-68% yield (68 mg and 76 mg). $[\alpha]^{20}_D = +15^o$ (c = 0.100, $CHCl_3$). $R_f = 0.63$ w/ 10%

acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 8.5 Hz, 2 H), 7.24 (d, *J* = 8.2 Hz, 2 H), 3.90 (s, 3 H), 3.25-3.16 (m, 1 H), 2.69 (d, *J* = 7.1 Hz, 2 H), 2.35-2.15 (m, 2 H), 1.67-1.42 (m, 4 H), 1.35-1.00 (m, 8 H), 0.82 (q, *J* = 7.0 Hz, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 210.0, 167.3, 150.6, 130.0, 128.4, 127.8, 52.2, 50.0, 43.8, 41.3, 36.1, 31.4, 29.7, 23.4, 22.7, 22.6, 14.1, 14.1. IR (neat): 2955, 2930, 2859, 1721, 1610, 1279, 1113 cm^{-1}. HRMS $C_{20}H_{30}O_3$ $(M+H)^+$ calcd. 319.2273, obsvd. 319.2272.

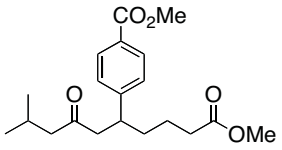
Table 4.3, entry 13 ((*S*)-methyl 4-(1-hydroxy-9-methyl-7-oxodecan-5-yl)benzoate) (**32**)



The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 10 mg Pd_2dba_3 (0.01 mmol, 0.03 equiv), and 7 mg ligand **21** (0.02 mmol, 0.07 equiv). (*E*)-9-Methyldec-5-ene-1,7-diol (65 mg, 0.35 mmol) and the aryldiazonium hexafluorophospate (240 mg 0.8 mmol, 2.2 equiv) derived from methyl 4-aminobenzoate were used, in a total of 3.5 mL DMF. The reaction was stirred for 15 h. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 10% acetone in hexanes to give the product as a yellow oil in 71-75% yield (80 mg and 84 mg). $[\alpha]^{20}_D$ = + 14^o (c = 0.107, $CHCl_3$). R_f = 0.08 w/ 10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 8.4 Hz, 2 H), 7.24 (d, *J* = 8.7 Hz, 2 H), 3.90 (s, 3 H), 3.58-5.53 (m, 2 H), 3.28-3.18 (m, 1 H), 2.69 (dd, *J* = 7.1, 7.0 Hz, 2 H), 2.20-1.99 (m, 3 H), 1.69-1.43 (m, 4 H), 1.29-1.05 (m, 3 H), 0.81 (d, *J* = 6.5 Hz, 3 H), 0.80 (d, *J* = 6.5 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 209.5, 167.2, 150.3, 130.0, 128.5, 127.8, 62.8,

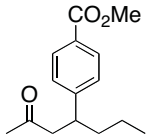
52.7, 52.2, 50.2, 41.0, 36.0, 32.7, 24.6, 23.8, 22.7, 22.6. IR (neat): 3512, 2953, 2870, 1717, 1610, 1436, 1280, 1113, 774, 668 cm^{-1}. HRMS $C_{19}H_{28}O_4$ $(M+Na)^+$ calcd. 343.1885, obsvd. 343.1880.

Table 4.3, entry 14 ((*R*)-methyl 4-(1-methoxy-9-methyl-1,7-dioxodecan-5-yl)benzoate) (**33)**



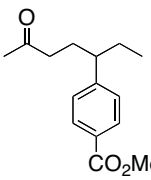
The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 11 mg Pd_2dba_3 (0.01 mmol, 0.04 equiv), and 7 mg ligand **21** (0.03 mmol, 0.09 equiv). (*Z*)-Methyl 7-hydroxy-9-methyldec-5-enoate (64 mg, 0.3 mmol) and the aryldiazonium hexafluorophospate (210 mg 0.7 mmol, 2.2 equiv) derived from methyl 4-aminobenzoate were used, in a total of 3 mL DMF. The reaction was stirred for 22 h. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 3% acetone in hexanes to give the product as a clear oil in 78-88% yield (82 mg and 92 mg). $[\alpha]^{20}_D = -10^o$ (c = 0.097, $CHCl_3$). R_f = 0.48 w/ 10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8.4 Hz, 2 H), 7.22 (d, *J* = 8.2 Hz, 2 H), 3.87 (s, 3 H), 3.59 (s, 3 H), 3.25-3.15 (m, 1 H), 2.66 (dd, *J* = 7.3, 6.9 Hz, 2 H), 2.24 – 1.93 (m, 5 h), 1.65-1.34 (m, 4 H), 0.77 (d, *J* = 6.5 Hz, 3 H), 0.76 (d, *J* = 6.6 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 209.2, 173.9, 167.2, 149.9, 130.1, 128.6, 127.8, 52.7, 52.2, 51.7, 50.1, 40.8, 35.6, 33.9, 24.6, 22.9, 22.7, 22.6. IR (neat): 2954, 1718, 1653, 1436, 1281, 1182, 1112, 668 cm^{-1}. HRMS $C_{20}H_{28}O_5$ $(M+H)^+$ calcd. 349.2015, obsvd. 349.2018.

Table 4.3, entry 15 ((*S*)-methyl 4-(2-oxoheptan-4-yl)benzoate) (**34**)



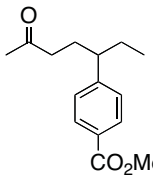
The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 14 mg Pd_2dba_3 (0.02 mmol, 0.03 equiv), and 10 mg ligand **21** (0.04 mmol, 0.07 equiv). (*E*)-Hept-3-en-2-ol (57 mg, 0.5 mmol) and the aryldiazonium hexafluorophospate (350 mg 1.1 mmol, 2.2 equiv) derived from methyl 4-aminobenzoate were used, in a total of 5 mL DMF. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 5% acetone in hexanes to give the product as a colorless oil in 70-77% yield (87 mg and 96 mg). $[\alpha]^{20}_{D}$ = + 21° (c = 0.123, $CHCl_3$). R_f = 0.39 w/10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 8.4 Hz, 2 H), 7.25 (d, *J* = 7.7 Hz, 2 H), 3.89 (s, 3 H), 3.26-3.16 (m, 1 H), 2.73 (d, *J* = 7.1 Hz, 2 H), 2.03 (s, 3 H), 1.65-1.48 (m, 2 H), 1.25-1.04 (m, 2 H), 0.84 (t, *J* = 7.3 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 207.5, 167.2, 150.4, 130.0, 128.5, 127.7, 52.2, 50.6, 41.0, 38.6, 30.8, 20.6, 14.1. IR (neat): 2956, 2931, 2872, 1719, 1610, 1436, 1729, 1113, 773, 668 cm^{-1}. HRMS $C_{15}H_{20}O_3$ $(M+H)^+$ calcd. 249.1491, obsvd. 249.1492.

Table 4.4, entry 1 ((+)-methyl 4-(6-oxoheptan-3-yl)benzoate) (**35**) from (*Z*)-alkene



The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 14 mg Pd_2dba_3 (0.02 mmol, 0.03 equiv), and 10 mg ligand **21** (0.04 mmol, 0.07 equiv). (*Z*)-Hept-4-en-2-ol (57 mg, 0.5 mmol) and the aryldiazonium hexafluorophospate (350 mg 1.1 mmol, 2.2 equiv) derived from methyl 4-aminobenzoate were used, in a total of 5 mL DMF. The reaction was stirred for 15 h. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 5% acetone in hexanes to give the product as a clear oil in 79% yield (98 mg and 98 mg). The γ-isomer shown was isolated along with approximately 3% of the β-isomer. $[\alpha]^{20}_D$ = + 4° (c = 0.113, $CHCl_3$). R_f = 0.39 w/ 10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 8.4 Hz, 2 H), 7.19 (d, *J* = 8.1 Hz, 2 H), 3.91 (s, 3 H), 2.52-2.43 (m, 1 H), 2.33-2.13 (m, 2 H), 2.07-1.93 (m, 4 H), 1.82-1.51 (m, 3 H), 0.75 (t, *J* = 7.3 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 209.0, 167.2, 150.6, 129.9, 128.4, 127.9, 52.2, 47.3, 41.7, 30.1, 30.0, 30.0, 12.2. IR (neat): 2958, 1718, 1609, 1436, 1280, 1113, 776, 709 cm^{-1}. HRMS $C_{15}H_{20}O_3$ $(M+H)^+$ calcd. 249.1491, obsvd. 249.1488.

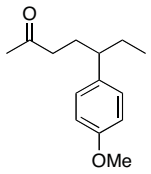
Table 4.4, entry 2 ((−)-methyl 4-(6-oxoheptan-3-yl)benzoate) (**35**) from (*E*)-alkene



The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 14 mg Pd_2dba_3 (0.02 mmol, 0.03 equiv), and 10 mg ligand **21** (0.04 mmol, 0.07 equiv). (*E*)-Hept-4-en-2-ol (57 mg, 0.5

mmol) and the aryldiazonium hexafluorophospate (350 mg 1.1 mmol, 2.2 equiv) derived from methyl 4-aminobenzoate were used, in a total of 5 mL DMF. The reaction was stirred for 15 h. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 5% acetone in hexanes to give the product as a colorless oil in 56-59% yield (70 mg and 73 mg). $[\alpha]^{20}_{D} = -4^{o}$ (c = 0.09, $CHCl_3$). The γ-isomer shown was isolated along with approximately 14% of the β-isomer. The ^{1}H NMR spectrum, see below, was compared to that of the product arising from the (*Z*)-isomer of the same alkene.

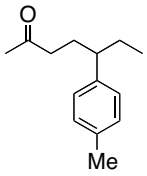
Table 4.4, entry 3 ((−)-5-(4-methoxyphenyl)heptan-2-one) (**36**)



The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 14 mg Pd_2dba_3 (0.02 mmol, 0.03 equiv), and 10 mg ligand **21** (0.04 mmol, 0.07 equiv). (*E*)-Hept-4-en-2-ol (57 mg, 0.5 mmol) and the aryldiazonium hexafluorophospate (320 mg 1.1 mmol, 2.2 equiv) derived from *p*-anisidine were used, in a total of 5 mL DMF. The reaction was stirred for 15 h. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 1% acetone in hexanes to give the product as a colorless oil in 56-65% yield (62 mg and 72 mg). $[\alpha]^{20}_{D} = -4^{o}$ (c = 0.093, $CHCl_3$). The γ-isomer shown was isolated along with approximately 9% of the β-isomer. R_f = 0.44 w/ 10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.02 (d, *J* = 8.7

Hz, 2 H), 6.84 (d, *J* = 8.5 Hz, 2 H), 3.80 (s, 3 H), 2.38-2.20 (m, 3 H), 2.03-1.90 (m, 4 H), 1.78-11.43 (m, 3 H), 0.76 (t, *J* = 7.4 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 209.5, 178.3, 158.1, 128.8, 113.9, 55.4, 46.5, 42.1, 30.5, 30.2, 12.4. IR (neat): 2960, 1714, 1617, 1512, 1248, 1117, 831, 668 cm^{-1}. HRMS $C_{14}H_{20}O_2$ $(M+Na)^+$ calcd. 243.1361, obsvd. 243.1364.

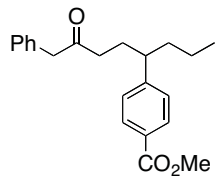
Table 4.4, entry 4 ((+)-5-(*p*-tolyl)heptan-2-one) (**37**)



The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 14 mg Pd_2dba_3 (0.02 mmol, 0.03 equiv), and 10 mg ligand **21** (0.04 mmol, 0.07 equiv). (*Z*)-Hept-4-en-2-ol (57 mg, 0.5 mmol) and the aryldiazonium hexafluorophospate (320 mg 1.1 mmol, 2.2 equiv) derived from *p*-toluidine were used, in a total of 5 mL DMF. The reaction was stirred for 15 h. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 1% acetone in hexanes to give the product as a colorless oil in 70-74% yield (72 mg and 76 mg). $[\alpha]^{20}_D$ = + 2^o (c = 0.120, $CHCl_3$). The γ-isomer shown was isolated along with approximately 10% of the β-isomer. R_f = 0.50 w/ 10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.12-7.07 (m, 2 H), 7.01-6.99 (m, 2 H), 2.38-2.17 (m, 6 H), 2.03-1.91 (m, 4 H), 1.78-1.50 (m, 3 H), 0.77 (t, *J* = 7.4 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 209.5, 141.8, 135.8, 129.3,

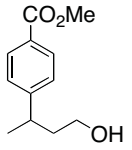
127.8, 47.0, 42.1, 30.3, 30.2, 30.1, 21.2, 12.4. IR (neat): 2960, 2926, 2873, 1717, 1514, 1357, 1161, 816, 668 cm^{-1}. HRMS $C_{14}H_{20}O$ $(M+Na)^+$ calcd. 227.1412, obsvd. 227.1413.

Table 4.4, entry 5 ((+)-methyl 4-(7-oxo-8-phenyloctan-4-yl)benzoate) (**38**)



The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 11 mg Pd_2dba_3 (0.01 mmol, 0.03 equiv), and 8 mg ligand **21** (0.03 mmol, 0.07 equiv). (*E*)-1-Phenyloct-3-en-2-ol (82 mg, 0.4 mmol) and the aryldiazonium hexafluorophospate (280 mg 0.9 mmol, 2.2 equiv) derived from methyl 4-aminobenzoate were used, in a total of 4 mL DMF. The reaction was stirred for 15 h. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 3% acetone in hexanes to give the product as a colorless oil in 64-68% yield (87 mg and 92 mg). $[\alpha]^{20}_D$ = + 5° (c = 0.107, $CHCl_3$). R_f = 0.39 w/ 10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8.4 Hz, 2 H), 7.32-7.25 (m, 4 H), 7.11-7.07 (m, 3 H), 3.91 (s, 3 H), 3.55 (s, 2 H), 2.57-2.46 (m, 1 H), 2.32-2.16 (m, 2 H), 2.03-1.92 (m, 1 H), 1.76-1.54 (m, 3 H), 1.25-1.00 (m, 2 H), 0.80 (t, *J* = 7.3 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 208.2, 167.3, 150.8, 134.3 130.0, 129.5, 128.9, 128.4, 127.9, 127.2, 52.2, 50.4, 45.1, 39.9, 39.1, 30.3, 20.7, 14.2. IR (neat): 2954, 2929, 2871, 1719, 1609, 1436, 1280, 1123, 774, 700, 668 cm^{-1}. HRMS $C_{22}H_{26}O_3$ $(M+Na)^+$ calcd. 361.1780, obsvd. 362.2784.

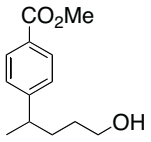
Figure 4.31 ((–)-methyl 4-(4-hydroxybutan-2-yl)benzoate derived from corresponding aldehyde, **39**)



The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 14 mg Pd_2dba_3 (0.02 mmol, 0.03 equiv), and 10 mg ligand **21** (0.04 mmol, 0.07 equiv). (*E*)-Crotonaldehyde (36 mg, 0.5 mmol) and the aryldiazonium hexafluorophospate (350 mg 1.1 mmol, 2.2 equiv) derived from methyl 4-aminobenzoate were used, in a total of 5 mL DMF. The reaction was stirred for 15 h. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 3% acetone in hexanes containing 0.1 % triethylamine to give an aldehyde product as a colorless oil in 73-78% yield (75 mg and 80 mg). This product was dissolved in MeOH, (4 mL) in a 20 mL scintillation vial equipped with a stir bar. The mixture was cooled to 0 ^oC. Sodium borohydride (21 mg, 0.55 mmol, 1.5 equiv) was added, and the resulting mixture was stirred for 30 min. The solvent was removed under reduced pressure, and the resulting residue was transferred to a separatory funnel using diethyl ether (10 mL) and water (10 mL). The aqueous layer was extracted with diethyl ether (2 x 15 mL), and the combined organic layers were washed with water (2 x 10 mL), and brine (1 x 10 mL). The organic layer was then dried over sodium sulfate, and concentrated under reduced pressure. The resulting mixture was purified using silica gel flash chromatography using 7% acetone in hexanes to give the alcohol product. $[\alpha]^{20}_D = -2^o$ (c = 0.107, $CHCl_3$). R_f = 0.31 w/ 20% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J*

= 8.7 Hz, 2 H), 3.90 (s, 3 H), 3.63-3.47 (m, 2 H), 2.98 (sextet, *J* = 7.7 Hz, 1 H), 1.91-1.83 (m, 2 H), 1.29 (d, *J* = 7 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 167.3, 152.6, 130.1, 128.3, 127.2, 61.1, 52.2, 40.8, 36.6, 22.3. IR (neat): 3431, 2962, 2927, 1718, 1701, 1652, 1506, 1280, 1115, 668 cm^{-1}. HRMS $C_{12}H_{16}O_3$ $(M+Na)^+$ calcd. 231.0997, obsvd. 231.1007.

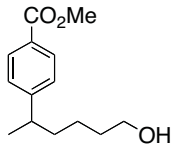
Figure 4.31 ((+)-methyl 4-(5-hydroxypentan-2-yl)benzoate derived from corresponding aldehyde, **40**)



The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 14 mg Pd_2dba_3 (0.02 mmol, 0.03 equiv), and 10 mg ligand **21** (0.04 mmol, 0.07 equiv). (*E*)-Pent-3-en-1-ol (43 mg, 0.5 mmol) and the aryldiazonium hexafluorophospate (350 mg 1.1 mmol, 2.2 equiv) derived from methyl 4-aminobenzoate were used, in a total of 5 mL DMF. The reaction was stirred for 15 h. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 3% acetone in hexanes containing 0.1 % triethylamine to give an aldehyde product as a colorless oil in 67-74% yield (74 mg and 81 mg). This product was dissolved in MeOH, (3 mL) in a 20 mL scintillation vial equipped with a stir bar. The mixture was cooled to 0 ^{o}C. Sodium borohydride (19 mg, 0.5 mmol, 1.5 equiv) was added, and the resulting mixture was stirred for 30 min. The solvent was removed under reduced pressure, and the resulting residue was transferred to a separatory funnel using diethyl ether (10 mL) and water (10

mL). The aqueous layer was extracted with diethyl ether (2 x 15 mL), and the combined organic layers were washed with water (2 x 10 mL), and brine (1 x 10 mL). The organic layer was then dried over sodium sulfate, and concentrated under reduced pressure. The resulting mixture was purified using silica gel flash chromatography using 7% acetone in hexanes to give the alcohol product. The product was isolated along with regioisomeric products. $[\alpha]^{20}_{D}$ = + 10 ^{o} (c = 0.125, $CHCl_3$). R_f = 0.33 w/ 20% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) (major product) δ 7.99-7.95 (m, 2 H), 7.27-7.24 (m, 2 H), 3.90 (s, 3 H), 3.60 (t , *J* = 6.6 Hz, 2 H), 2.78 (sextet, *J* = 6.9 Hz, 1 H), 1.75-1.37 (m, 4 H), 1.27 (d, *J* = 7 Hz, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) (all resonances) δ = 153.1, 130.1, 130.0, 129.9, 129.8, 128.2, 128.0, 127.3, 127.3, 126.3, 125.9, 125.7, 63.1, 62.4, 61.1, 52.2, 48.0, 44.4, 40.1, 39.2, 3.1, 24.4, 32.6, 31.0, 29.8, 24.1, 22.3, 12.2. IR (neat): 3420, 2954, 1719, 1436, 1280, 1114, 773, 668 cm^{-1}. HRMS $C_{13}H_{18}O_3$ $(M+Na)^+$ calcd. 245.1154, obsvd. 245.1137.

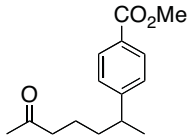
Figure 4.31 ((+)-methyl 4-(6-hydroxyhexan-2-yl)benzoate derived from corresponding aldehyde, **41**)



The general procedure for the preparation of methyl **22** was used with the following modifications. The ligated catalyst mixture contained 14 mg Pd_2dba_3 (0.02 mmol, 0.03 equiv), and 10 mg ligand **21** (0.04 mmol, 0.07 equiv). (*E*)-Hex-4-en-1-ol (50 mg, 0.5 mmol) and the aryldiazonium hexafluorophospate (350 mg 1.1 mmol, 2.2 equiv) derived from methyl 4-aminobenzoate were used, in a total of 5 mL DMA. The reaction

was stirred for 15 h. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 3% acetone in hexanes containing 0.1 % triethylamine to give an aldehyde product as a colorless oil in 56-61% yield (65 mg and 71 mg). This product was dissolved in MeOH, (3 mL) in a 20 mL scintillation vial equipped with a stir bar. The mixture was cooled to 0 ^{o}C. Sodium borohydride (17 mg, 0.43 mmol, 1.5 equiv) was added, and the resulting mixture was stirred for 30 min. The solvent was removed under reduced pressure, and the resulting residue was transferred to a separatory funnel using diethyl ether (10 mL) and water (10 mL). The aqueous layer was extracted with diethyl ether (2 x 15 mL), and the combined organic layers were washed with water (2 x 10 mL), and brine (1 x 10 mL). The organic layer was then dried over sodium sulfate, and concentrated under reduced pressure. The resulting mixture was purified using silica gel flash chromatography using 7% acetone in hexanes to give the alcohol product. The product was isolated along with regioisomeric products. $[\alpha]^{20}_{D}$ = + 10 ^{o} (c = 0.105, $CHCl_3$). R_f = 0.33 w/ 20% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) (major product) δ 7.96 (d, *J* = 8.2 Hz, 2 H), 7.21 (d, *J* = 8.7 Hz, 2 h), 3.90 (s, 3 H), 3.63-3.51 (m, 2 H), 2.75 (sextet, *J* = 7.2 Hz, 1 H), 1.83-1.17 (m, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$) (all resonances) δ = 167.4, 153.3, 151.4, 129.9, 129.9, 128.1, 128.0, 127.2, 63.1, 63.0, 52.2, 48.0, 40.3, 38.1, 32.9, 32.6, 31.0, 30.0, 24.0, 22.3, 12.3. IR (neat): 3446, 2933, 2873, 1718, 1700, 1559, 1457, 1114, 668 cm^{-1}. HRMS $C_{14}H_{20}O_3$ $(M+Na)^+$ calcd. 259.1310, obsvd. 259.1310.

Figure 4.32 ((+)-methyl 4-(6-oxoheptan-2-yl)benzoate) (**43**)



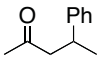
The general procedure for the preparation of **22** was used with the following modifications. The ligated catalyst mixture contained 14 mg Pd_2dba_3 (0.02 mmol, 0.03 equiv), and 10 mg ligand **21** (0.04 mmol, 0.07 equiv). (*E*)-Hept-5-en-2-ol (57 mg, 0.5 mmol) and the aryldiazonium hexafluorophospate (350 mg, 1.1 mmol, 2.2 equiv) derived from methyl 4-aminobenzoate were used, in a total of 5 mL DMF. The reaction was stirred for 15 h. Following the aqueous workup described above and concentration, the product was purified by silica gel flash chromatography using 3% acetone in hexanes to give **43** as a colorless oil in 48-54% yield (60 mg and 67 mg). $[\alpha]^{20}_D$ = + 8° (c = 0.230, $CHCl_3$). R_f = 0.39 w/ 10% acetone in hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2 H), 7.24 (d, *J* = 8.2 Hz, 2 h), 3.90 (s, 3 H), 2.75 (sextet, *J* = 7.0 Hz, 1 H), 2.38 (t, *J* = 6.9 Hz, 2 H), 2.08 (s, 3 H), 1.61-1.35 (m, 4 H), 1.24 (d, *J* = 6.9 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 209.1, 153.0, 130.0, 130.0, 128.2, 127.2, 52.2, 43.8, 40.2, 37.7, 30.1, 22.2, 22.1. IR (neat): 2953, 1713, 1609, 1435, 1275, 1111, 1019, 857, 775, 708 cm^{-1}. HRMS $C_{15}H_{20}O_3$ $(M+Na)^+$ calcd. 271.1310, obsvd. 271.1315.

Preparation of racemic products in Tables 4.3-4.4 and Figure 4.31

The procedure for the preparation of each product in Tables 4.3-4.4 and Figures 4.31 and 4.32 was used with the modification that the ligand was omitted from the reaction mixture. The reactions were performed in otherwise identical fashion as the

enantiomerically enriched products. The products were worked up and purified in the same fashion as described for the enantiomerically enriched products.

Procedure for the preparation of 4-phenylpentan-2-one (**11**) under oxidative Heck conditions

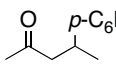
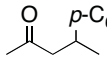
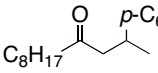
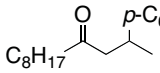
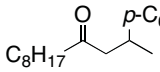
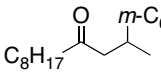
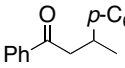
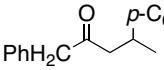
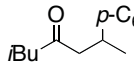
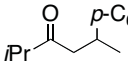
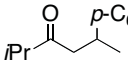
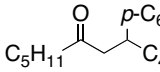
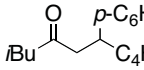
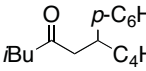
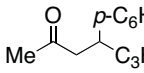


To a dry 5 mL Schlenk flask equipped with a stir bar was added *bis*-acetonitrile palladium (II) toluenesulfonate (2 mg, 0.004 mmol, 0.04 equiv), copper (II) trifluoromethanesulfonate (1 mg, 0.004 mmol, 0.004 equiv), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (**21**) (3 mg, 0.01 mmol, 0.1 equiv), and 3 Å MS (13 mg). The flask was placed under an N_2 atmosphere. To this mixture was added DMF (0.4 mL), and the mixture was stirred for 10 min. To this mixture was added 100 μL of the mixture containing (*E*)-pent-3-en-2-ol and tetradecane (**10**) (0.1 mmol, 1 equiv). A three-way joint was fitted with a balloon of O_2 and attached to the flask. The apparatus was evacuated and refilled with O_2 three times. To the stirred mixture was added phenylboronic acid (24 mg, 0.2 mmol, 2 equiv) in DMF (0.5 mL), and the mixture was heated to 40 ^{o}C in an oil bath. The mixture was stirred for 21 h. The mixture was then passed through a silica gel pipet with diethyl ether, and analyzed for product formation and enantiomeric ratio by gas chromatography.

Determination of enantiomeric ratio

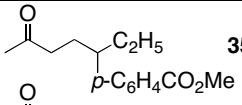
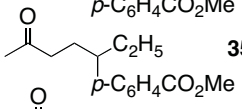
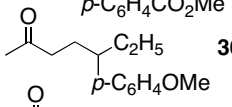
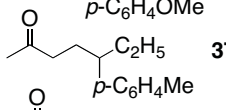
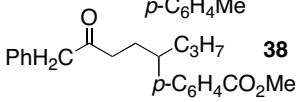
The enantiomeric ratio of each of the products shown in Tables 4.3-4.4 and Figure 4.31 was determined by chiral chromatography as described in Tables 4.5-4.8.

Table 4.5. Determination of enantiomeric ratios of products shown in Table 4.3.

entry	compound[a]	conditions	retention time	er
1	 **22**	SFC, AD-H column 5-50% MeOH, 2 mL/min	3.3 and 3.7 min	93:7
2	 **23**	SFC, AD-H column 5-50% MeOH, 2 mL/min	3.5 and 3.9 min	91:9
3	 **24**	SFC, AD-H column 5-50% MeOH, 2 mL/min	3.9 and 5.5 min	97:3
4	 **25**	SFC, AD-H column 5-50% MeOH, 2 mL/min	5.0 and 6.3 min	97:3
5[b]	 **25**	SFC, AD-H column 5-50% MeOH, 2 mL/min	4.8 and 6.1 min	4:96
6[b]	 **26**	SFC, AD-H column 5-15% *i*PrOH, 1 mL/min	14.3 and 14.7 min	3:97
7[b]	 **27**	SFC, AD-H column 5-50% MeOH, 2 mL/min	5.6 and 7.8 min	3:97
8	 **28**	SFC, AD-H column 5-50% MeOH, 2 mL/min	4.9 and 6.0 min	97:3
9	 **29**	SFC, AD-H column 5-50% MeOH, 2 mL/min	3.6 and 4.9 min	96:4
10	 **30**	SFC, AD-H column 5-50% MeOH, 2 mL/min	2.9 and 3.6 min	95:5
11[b]	 **30**	SFC, AD-H column 5-50% MeOH, 2 mL/min	3.7 and 4.3 min	4:96
12	 **31**	SFC, AD-H column 5-50% *i*PrOH, 2 mL/min	4.0 and 4.5 min	95:5
13	 **32**	SFC, AD-H column 5-50% *i*PrOH, 2 mL/min	6.0 and 6.8 min	94:6
14[b]	 **33**	SFC, AD-H column 5-50% *i*PrOH, 2 mL/min	4.2 and 4.4 min	7:93
15	 **34**	SFC, AD-H column 5-50% MeOH, 2 mL/min	3.5 and 3.8 min	4:96

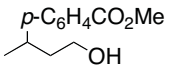
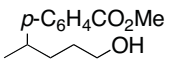
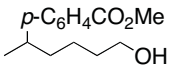
[a]All compounds are products of the asymmetric Heck reaction using (*E*)-allylic alcohol starting materials unless otherwise noted. [b]Compounds are the products of the asymmetric Heck reaction using (*Z*)-allylic alcohol starting materials.

Table 4.6. Determination of enantiomeric ratios of products shown in Table 4.4.

entry	compound[a]	conditions	retention time	er
1[b]	 **35**	SFC, AD-H column 5-15% *i*PrOH, 1 mL/min	13.2 and 14.9	96:4
2	 **35**	SFC, AD-H column 5-15% *i*PrOH, 1 mL/min	14.5 and 14.9	10:90
3	 **36**	To be determined	xx and xx min	xx:xx
4[b]	 **37**	SFC, AD-H column 1-50% MeOH, 2 mL/min	22.8 and 27.7 min	97:3
5	 **38**	SFC, AD-H column 5-50% *i*PrOH, 2 mL/min	5.3 and 5.4 min	6:94

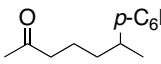
[a]All compounds are products of the asymmetric Heck reaction using (*E*)-allylic alcohol starting materials unless otherwise noted. [b]Compounds are the products of the asymmetric Heck reaction using (*Z*)-allylic alcohol starting materials.

Table 4.7. Determination of enantiomeric ratios of alcohol derivatives of products shown in Figure 4.31.

entry	compound[a]	conditions	retention time	er
1	 **39**	SFC, AS-H column 5-15% *i*PrOH, 1 mL/min	4.4 and 4.8 min	~40:60
2	 **40**	SFC, AS-H column 5-15% *i*PrOH, 1 mL/min	14.0 and 14.6 min	3:97
3	 **41**	SFC, AD-H column 5-50% *i*PrOH, 2 mL/min	5.9 and 6.1 min	94:6

[a]All compounds are alcohol derivatives of aldehydes synthesized using the asymmetric Heck reaction using (*E*)-allylic alcohol starting materials

Table 4.8. Determination of enantiomeric ratio of product **43**.

entry	compound	conditions	retention time	er
1	 **43**	SFC, AD-H 5-50% *i*PrOH, 2 mL/min	4.0 and 4.2 min	96:4

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